A STUDY OF METABOLIC BONE DISEASE

IN CHRONIC LIVER DISEASE

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By

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Dedicated

to

my Family

&

Teachers

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Dr. Avinash Singh

ABBREVATIONS

1.	PBC	-	Primary biliary cirrhosis
2.	IGF	-	Insulin Like Growth Factor
3.	DEXA	-	Dual Energy Xray Absorptiometry
4.	IL	-	Interleukin
5.	TNF	-	Tumour Necrosis Factor
6.	CT	-	Computerized Tomography
7.	MRI	-	Magnetic Resonance Imaging
8.	BMD	-	Bone Mineral Density
9.	LDL	-	Low Density Lipoprotein
10.	PTH	-	Parathyroid Hormone
11.	CTP	-	Child Turcotte Pugh
12.	SGOT	-	Serum Glutamic oxaloacetic Transaminase
13.	SGPT	-	Serum Glutamic Pyruvate Transaminase
14.	INR	-	International Normalized Ratio
15.	ALP	-	Alkaline Phosphatase
16.	HE	-	Hepatic Encephalopathy
17.	NASH	-	Non-alcoholic Steato hepatitis
18.	HCV	-	Hepatitis C virus
19.	HBV	-	Hepatitis B virus
20.	PTH	-	Parathyroid hormone
21.	MELD	-	Model for end liver disease

ABSTRACT

Introduction: Chronic liver disease is significant cause for morbidity and mortality worldwide. BMD loss is present in all etiologies of cirrhosis. The development of metabolic bone disease in patients with cirrhosis has, been directly related to the duration and severity of cirrhosis.

Aim of Study: To study prevalence of metabolic bone disease in chronic liver disease according to aetiology of cirrhosis and to assess the improvement in BMD after treatment on 6 month.

Materials & methods:

The present study was conducted in Dayanand Medical College and Hospital, Ludhiana in which 96 patients of cirrhosis were enrolled, to find out the presence of metabolic bone disease and the one who found to be having hepatic osteodystrophy is being treated and evaluated again after 6 months to see the response of therapy.

Results: The mean of patients was 52±8.71 years, most common etiology is alcohol 53 patients (55.2%) followed by NASH 22 patients (22.9%), the majority of patients 42(43.8%) fall into CTP score B, 32(33.3%) was in CTP class A and 22(22.9%) was in CTP class C. 51 patients (53%) were found to have low BMD. Significant association was found between low BMD and age of patients, 64% patients of more than 60 years of age had shown low BMD. Significant association was also found between severity of cirrhosis and low BMD as 72.7% patients of CTP class C had low BMD while only 34 % patients from CTP class A had low BMD. 26 patients (51%) had shown improvement in BMD after treatment. 82.3% patients of cirrhosis duration <30 months had shown improvement in BMD after treatment while only 32 % patients of cirrhosis duration >30 months had improvement in BMD.

Conclusion: The prevalence of metabolic bone disease is >50% in cirrhosis and it increases linearly with severity and duration of cirrhosis and is more common in age >60 years. The metabolic bone disease detected and treated the better is outcome and prevention of fractures.

Keywords: Metabolic Bone Disease, liver cirrhosis

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INTRODUCTION

Literature database outlines Global Burden of Liver Disease estimates roughly 1.03 million deaths per year in the world wide and over a million deaths in 2010 by cirrhosis.[1] Cirrhosis (chronic liver disease) represents a disorder which causes progressive hepatic fibrosis characterized by distorted liver architecture and the formation of nodules which are regenerative. Cirrhosis of any cause is usually not reversible when it is in the advanced stages at which the only option available may be liver transplantation. However, in recent times reversal of cirrhosis has been reported in several forms of liver disease following treatment of the underlying cause if detected in its early stages.

Chronic liver disease is a significant cause for morbidity and mortality worldwide and may lead to various complications, such as liver failure, portal hypertension, hepatorenal syndrome, ascites, encephalopathy and oesophageal variceal haemorrhage. Chronic liver disease is also a risk factor for osteoporosis, osteopenia and bone fractures.[2] Hepatic osteodystrophy is a term used to describe metabolic bone diseases, such as osteopenia, osteoporosis and osteomalacia, seen at various degrees due to chronic liver disease.[3] While osteomalacia is a rare condition accompanying chronic liver disease,[4] osteoporosis is more common (11–55%).[3–5] Prevalence of hepatic osteodystrophy in cirrhotic patients varies from 12 to 70% in various studies and osteoporosis is common among all cirrhotic patients regardless of the liver disease etiology.[6]

Hepatic osteodystrophy is a bone disease of multifactorial origin associated with chronic liver disease.[7] Cholestatic liver disease has higher incidence of hepatic osteodystrophy than non cholestatic liver disease, but BMD loss is present in all etiologies of cirrhosis.[8] There is scanty data from India on hepatic osteodystrophy. Recently a study in Mumbai showed high prevalence of osteodystrophy among patients with cirrhosis.[9]

Among the cirrhotic patients increased prevalence of osteopenia and osteoporosis has been demonstrated in patients with chronic liver disease of different aetiologies in the recent times.[10] Osteoporosis is the only complication that persists for years after liver transplantation.[11] Due to osteoporosis most of the fractures are overlooked in non cirrhotic individuals as they are able to walk than cirrhotic patients who will be hospitalized.[12] Osteoporosis denotes a state in which the bones become porous resulting in increased risk for fractures.[13] However, osteoporosis often remains unnoticed due to indolent clinical features and is often ignored in the presence of other complications.

Some of the common cause for cirrhosis are[14]

1. Alcoholic liver disease
2. Viral hepatitis B & C
3. Autoimmune hepatitis
4. Hereditary hemochromatosis
5. Wilson's disease
6. Alfa-1 antitrypsin deficiency
7. Non-alcoholic fatty liver disease
8. Primary biliary cirrhosis
9. Primary sclerosing cholangitis

Complications of cirrhosis include[14]

1. Variceal bleed
2. Hepatic encephalopathy
3. Ascites
4. Spontaneous bacterial peritonitis
5. Hepatorenal syndrome
6. Hepatopulmonary syndrome
7. Hepatocellular carcinoma

The development of metabolic bone disease in patients with cirrhosis has, in most reports, been directly related to the duration and severity of cirrhosis and to the intensity and duration of jaundice. However, the mechanisms which cause osteodystrophy in patients with cirrhosis are not well understood. The plasma concentrations of vitamin D metabolites and calcium are usually normal. Biochemical and bone histomorphometric studies suggest that these patients, particularly in the precirrhotic stage, have a "low-turnover" osteoporosis, in which bone formation is inhibited and bone resorption is low or normal, although the mechanism(s) causing these changes are not known.[15]

It was initially proposed that decreased bile salt flow, leading to malabsorption of vitamin D, was responsible for the development of osteoporosis. However, this hypothesis is most likely incorrect given the observations that the plasma levels of calcidiol (25-hydroxyvitamin D) and calcitriol (1,25 dihydroxyvitamin D) are normal in PBC patients with osteoporosis and that vitamin D replacement in the group of cases with decreased plasma concentrations will not improve the severity of osteodystrophy.

Genetic causes for osteopenia in PBC like polymorphisms in vitamin D receptor[16] polymorphisms in IGF-1 gene and polymorphisms in collagen type Ia gene have been proposed, but none of the genetic variations were proven to be associated in most of the studies.

Dual-energy X-ray absorptiometry (DEXA) is the gold standard commonly used to measure bone mass because it is accurate and can measure multiple skeletal sites[17]; most commonly applied to the lumbar spine and femoral neck. DEXA made it possible to rapidly and precisely quantify the amount of bone in the relevant fracture sites.[18] The high level of precision of this technique allows not only for diagnosis, but also for monitoring response to treatment. It is non-invasive, accurate, rapid and safe.[19]

AIMS AND OBJECTIVES

- To study prevalence of metabolic bone disease in chronic liver disease.
- To study the relative prevalence of metabolic bone disease according to aetiologies of cirrhosis.
- To study the improvement in Bone mineral density after treatment on 6 month follow up.

REVIEW OF LITERATURE

Osteodystrophy is a complication in patients with chronic hepatopathy, especially in those affected by chronic cholestasis. Metabolic bone disease usually manifests as osteopenia and osteoporosis. This bone disorder must be evaluated and detected early in all cirrhotic patients to minimize the risk of fractures and improve the quality of life.

EPIDEMIOLOGY

Various international studies have shown the overall incidence of metabolic bone disease in cirrhosis to be between 11% to 48%, and fracture risk due to the bone disease to be between 3%-44%.

Some of the studies which has shown the prevalence are

1. Goral et al. 2010[15] – frequency of osteodystrophy was 37% in patients with cirrhosis of mixed etiology
2. Wariaghli et al. 2010[16] – frequency of osteodystrophy was 45.3% in patients with cirrhosis of mixed etiology
3. Sokhi et al. 2004[15,16] – frequency of osteoporosis was 11.5% and osteopenia was 34.6% in patients cirrhosis of mixed etiology

Chronic liver diseases which are known to cause hepatic osteodystrophy include, cholestatic liver diseases like primary biliary cirrhosis and primary sclerosing cholangitis.[14] Hepatic osteodystrophy can also occur in cirrhosis of any aetiology.

PATHOGENESIS

The pathogenesis of hepatic osteodystrophy in patients with liver cirrhosis has not been completely understood. Several factors which includes- decreased bone formation and increased bone resorption has been recognized in liver cirrhosis. Studies have shown that increase in proinflammatory cytokines, low insulin-like growth factor, and low vitamin K lead to alterations in bone metabolism. Cytokines which are increased in cirrhosis are IL-1, IL-6 and TNF-alfa.[20] Serum osteocalcin levels decreases depending on reduction of osteoblast function. A decrease in serum osteocalcin levels and an increase in deoxypyridinoline (DPD)

level have been observed in chronic liver disease which is the reason for the low turnover of bone mass.

Other factors responsible for reduced bone mineral deposition are

1. Vitamin K deficiency – is required for osteoblasts to synthesize osteocalcin-bone matrix protein. VitaminK deficiency leads to osteopenia in primary biliary cirrhosis and by supplementing it bone loss can be prevented.[16]
2. IGF-1 deficiency – is required for osteoblast differentiation and proliferation. IGF-1 deficiency occurring in cirrhosis and cholestatic liver disease cause osteoblast dysfunction and osteopenia.[20]
3. Hyperbilirubinemia- rise in indirect hyperbilirubinemia has shown impair osteoblast function in animal models.[16] But this is not proven in human studies.

ROLE OF CYTOKINE IN HEPATIC OSTEODYSTROPHY

Interleukin 1, Interleukin 6, TNF-alfa which is increased in chronic liver disease activates receptor activator of nuclear factor κB ligand/osteoprotegerin, which regulates bone formation by modulating osteoclast activity. Receptor activator of nuclear factor κB ligand/osteoprotegerin is upregulated in chronic liver disease which is activated by the increased cytokines and cause increased bone resorption.[20]

Factors which increase the risk of osteodystrophy in cirrhotic patients include.[16]

1. Hypogonadism
2. Vitamin D deficiency
3. Alcohol consumption
4. Chronic steroid treatment
5. Low body mass index

Contribution of vitamin D

Vitamin D has a variety of actions on minerals like calcium, phosphate, and bone metabolism. Vitamin D has an important biological effect on the enterocyte to promote differentiation and causes the intestinal absorption of calcium and phosphorus, which in turn promote bone mineralization. In high vitamin D concentrations and when there is calcium and phosphate deficiency, it also causes stimulation of bone resorption, which helps in the maintaince of supply of these ions to other tissues.[21] Vitamin D is synthesized in the skin with exposure of ultraviolet rays from the sun; ultraviolet rays convert 7-dehydrocholesterol to vitamin D. Anyone with reduced exposure to the sun is prone to vitamin D deficiency. Calcidiol, is formed in the liver before being converted in the kidneys into metabolic active vitamin D (calcitriol).

Gastrointestinal causes of vitamin D deficiency include gastrointestinal malabsorption, associated with disorders of the small intestine, pancreatic diseases resulting in decreased absorption of vitamin D and hepatobiliary disease causes depletion of endogenous 25OHD stores due to abnormal enterohepatic circulation. Malabsorption of vitamin D results as a consequence of steatorrhea, which reduces fat emulsification and chylomicron-facilitated absorption.[21] Vitamin D deficiency may be associated with rickets or osteomalacia. Patients affected are asymptomatic or may exhibit a reduction in bone volume rather than causing defective bone mineralization.

In liver failure, the levels of 25-OH vitamin D can be reduced due to impaired synthesis. However, liver function needs to be severely compromised for it to cause reduced 25-OH vitamin D synthesis.[16] Subclinical vitamin D insufficiency is common in the setting of chronic liver disease and could contribute to the formation of osteoporosis or osteopenia by decreasing absorption of calcium.[21]Vitamin D deficiency is usually associated with secondary hyperparathyroidism, and there is increased bone turnover and accelerated loss of bone mass. Factors

which contribute to vitamin D deficiency include Intestinal malabsorption, altered enterohepatic circulation of vitamin D and reduced skin synthesis in patients with jaundice.

CLINICAL FEATURES

Patients with metabolic bone disease are usually asymptomatic and they are picked up during routine screening.

When symptoms do occur, they are related to fractures. The most common fractures are vertebral fractures, two-thirds of which are asymptomatic and are diagnosed as incidental findings on a chest or abdominal x-ray. In some patients, vertebral fractures may result in loss of height, kyphosis, or acute back pain. Other fractures seen in patients with osteoporosis include hip fractures and distal radius fractures

FRACTURE RISK ASSESSMENT

Facture risk has to determined in patients with metabolic bone disease irrespective of the cause. Patients with osteoporosis and osteopenia are at increased risk for facture.[22] Risk factors independent of bone mineral density include

1. Previous history of fracture
2. Increased age
3. Long-term glucocorticoid therapy
4. Low body weight < 58 kg
5. Family history of hip fracture
6. Smoking
7. Excess alcohol intake

DIAGNOSIS OF METABOLIC BONE DISEASE

Bone mineral density determines the bone strength. Determinants of bone strength, which are not dependent on bone mineral density are bone turn over, microarchitecture of bone like trabecular thickness, cortical thickness and cortical porosity, matrix properties and mineralizaton.

Investigation for bone strength will give an insight on the pathogenesis of osteoporosis and osteopenia and gives a better understanding on the treatment given for osteoporosis. Investigations like micro CT and MRI are being developed which can discern individual trabeculae are being developed. With these investigations fracture risk can be accurately gauged. As of now the gold standard for the diagnosis of metabolic bone disease is by DEXA scan.[21]

Bone mineral density testing — BMD testing is the most commonly used clinical test to diagnose osteoporosis, osteopenia, predict the risk for fracture, and monitor response to therapy. BMD testing can be done on various sites of the body and predict fracture risk. Dual-energy x-ray absorptiometry (DEXA SCAN) of the spine, hip, and forearm is the method for diagnosis of osteoporosis.[23] Serial monitoring of bone mineral density over a period is essential because

1. There has been a strong correlation between bone mineral density measured by DEXA scan and mechanical strength.
2. Studies have shown relationship between bone mineral density by DEXA scan and fracture risk.
3. Randomized clinical trials have shown drug therapy based on the bone mineral density measurement has reduced fracture risk.
4. Accuracy and precision of bone mineral density measured by DEXA scan is very good.
5. Radiation exposure with DEXA scan is very low.

Dual-energy x-ray absorptiometry technology- A typical DEXA scan machine consists of a padded table on which the patient should lie and a movable C-arm with an x-ray tube under the patient and a detector above the patient. The x-ray tube, which is below the patient generates photon beams of two different energy levels, for which is called "dual-energy" source. A collimator below the table controls the scatter of the photons and directs the photons towards the area of interest. The difference in attenuation that is the reduction in intensity of

the two photon beams as they go through body tissue of variable composition and distinguishing bone from soft tissue and allows quantification of bone mineral density. Denser and thicker tissue contains more electrons and will not allow many photons to pass through to the detector. A computer which is specially designed with its proprietary software designed by each manufacturer forms a complete DEXA scan.

Radiation exposure to the patient is very minimal, usually of a similar magnitude to daily background radiation. Radiation which is scattered beyond the edge of the DEXA table is negligible. Shielding of the technologist or the room is not necessary. But as a safety precaution, the technologist doing the DEXA scan should typically not sit within three feet of the table edge when the patient is being scanned.

DEXA measures bone mineral content (in gms) and bone area (in square centimetres), then calculates "areal" BMD in g/cm2 by dividing bone mineral content and bone area. T-score, the value used for diagnosis of osteoporosis, is calculated by subtracting the mean BMD of a young-adult reference population from the patient's BMD and dividing by the standard deviation (SD) of young-adult population. Z-score, used to compare the patient's BMD to a population of peers, is calculated by subtracting the mean BMD of an age-, ethnicity-, and sex-matched reference population from the patient's BMD and dividing by the SD of the reference population. The mean BMD and SD of the reference populations used for these calculations is a critical variable in the determination of T-score. There are significant differences in the technologies used by different manufacturers and sometimes different models of DEXA made by the same manufacturer. Manufacturers use different methods for creating dual photon beams (e.g. K-edge filtering and voltage switching), different bone edge detection algorithms, different assumptions on body size and tissue composition, different calibration, and different types of photon detectors. Photon beams have different configurations, e.g. pencil beam and fan beam. The bone regions of interest (ROI) measured may be different, especially so with

the femoral neck. The reference databases used to calculate T-scores and Z-scores may be different. For all of these reasons, it is not possible to make quantitative comparisons of BMD measured on different instruments, especially those made by different manufacturers, unless a cross-calibration study has been done

According to the World Health Organization (WHO) criteria [24] Normal BMD is represented by a T score of more than -1. Osteopenia (low bone mass) is represented by a T score between-1 and -2.5. Osteoporosis is presented by a T score less than -2.5. established osteoporosis is represented by a T score of less than -2.5 and a previous history of a fragility fracture

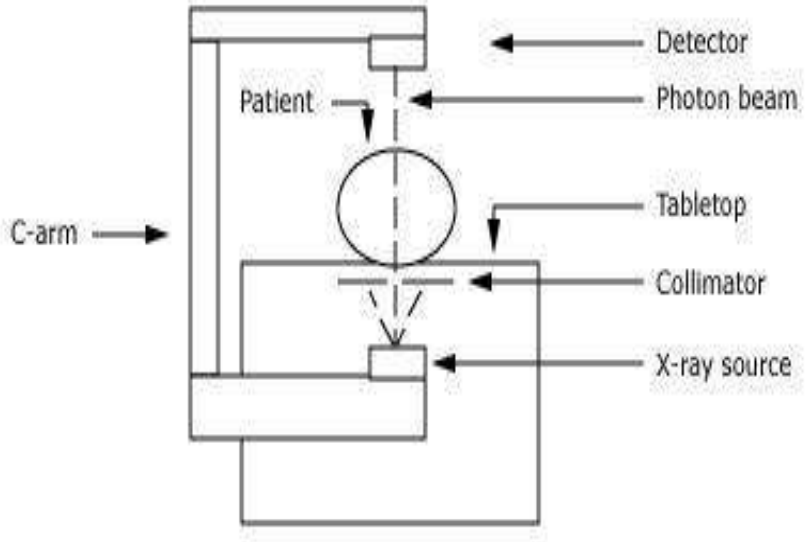

Figure 1 – dual energy x-ray absorptimetry.

Other methods to analyze bone mineral density

1. **Quantitative CT** – cortical and trabecular bone can be assessed by determining the volume of bone density. It can measure the bone density of hip and spine. This test can be used to assess the treatment response and is also being used is research setup. This method is not used for routine screening. Drawbacks of this test are, it cannot assess the risk of fracture and is a very expensive test.

2. **Ultrasound** - Patients at risk for osteoporosis can be identified with use of quantitative ultrasound, which is a reasonable predictor of fracture risk. This method can be used in mass screening setup and there is no risk of radiation. But ultrasound threshold cut off for DEXA score has not been having good sensitivity and specificity. This test cannot be used as confirmatory test and always one has do DEXA scan in suspected patients to confirm low bone mineral density. Since with ultrasound only the peripheral sites can be measured it cannot be used as a tool for follow up of patients who are on therapy. In current clinical practice quantitative ultrasound can only be used in mass screening and clinical research.

SITE OF MEASUREMENT OF BONE MINERAL DENSITY

Most common site for measurement of bone mineral density are HIP and SPINE. Spine measurement is more accurate and fracture risk can be assessed more precisely. In patients with cirrhosis and ascites, measurement of bone mineral density of spine can be falsely positive, due to the fluid in the abdomen. In these patients with ascites measurement of bone mineral density from the hip will be useful to assess the risk of fracture.[24]

Other sites of bone mineral density measurement include the peripheral site like calcaneum and wrist. Methods by which the measurement can be done are portable DEXA scan, x-ray absorptiometry and ultrasound.

These methods by which the peripheral bone mineral density is measured are not validated and the only method validated by the WHO is DEXA scanning of the hip or spine. Only place where the peripheral measurement is used is, in the setting of mass screening.

SCREENING FOR BONE MINERAL DENSITY LOSS

Screening for osteoporosis has to be done in all patients with chronic liver disease. DEXA scan should be advised once a year and follow up of patients on treatment for osteoporosis or osteopenia can be done with DEXA scan every 2 years.[25] There are few studies showing the

incidence of osteoporosis in chronic liver disease with varying etiology to be between 11 to 48%. So, screening for osteodystrophy in cirrhotic patients can reduce the fragile fractures and can lead to improvement in the quality of life. Post liver transplant patients are prone for bone disease and increased risk of fractures, so it is advisable to screen all patients awaiting liver transplant, in order to give them the appropriate treatment and reduce fracture risk.

TREATMENT

General treatment includes non pharmacologic measures like diet rich in vitamin D, light exercises and smoking cessation .Smoking is major risk factor for osteodystrophy and smoking cessation considerably decreases the risk of fractures. Calcium and vitamin D supplementation should be done to maintain bone density. Calcium in the dose of 1000 mg /day and the dose of vitamin D is 800 U/day.[26]

Pharmacological therapy for metabolic bone disease

Bisphosphonates — Alendronate (10 mg/day or 70 mg once weekly [orally]) or risedronate (5 mg/day, 35 mg once weekly, or 150 mg once monthly), and ibandronate (150 mg once monthly [orally] or 3 mg intravenously every three months).[27] Zoledronic acid (ZA), 5 mg administered intravenously (IV) once yearly, is also effective for osteodystrophy. Severe esophagitis can occur with this group of drugs and it can be prevented by taking large amounts of water and being upright for 1 hour. Bisphosponates are the main treatment in patients with severe metabolic bone disease, even though there is very limited data on its use in cirrhosis.

Etidronate was licensed for use in many countries for patients with established vertebral osteoporosis, but at present it is barely used in the treatment of primary and secondary osteoporosis. By contrast, alendronate is a worldwide-approved drug and it is well established for the treatment of osteoporosis. However, its weekly administration has prompted researchers to search a bisphosphonate with less frequent dosing intervals, such as a once-monthly oral regimen.[26]

This strategy could have an impact on adherence and persistence with treatment, since a growing body of evidence suggests that adherence with daily and weekly oral bisphosphonates is suboptimal with an impaired therapeutic efficacy. Thus, a less frequent intermittent administration may help to overcome these deficiencies.[27]

Selective estrogen receptor modulators- Raloxifene is a tissue selective estrogen receptor modulator (SERM) that is used for the prevention and treatment of osteoporosis (27). It increases bone mineral density and reduces the risk of vertebral fractures. Raloxifene also appears to lower the risk of breast cancer, does not stimulate endometrial hyperplasia or vaginal bleeding, and increases the risk of venous thromboembolism. Although it decreases serum total and low-density-lipoprotein (LDL) cholesterol concentrations, raloxifene does not appear to affect the risk of coronary heart disease. Raloxifen is one of the first-line drugs for prevention of osteoporosis. However, it is somewhat less effective than estrogen and bisphosphonates, although direct fracture prevention comparisons are lacking. There are nonskeletal considerations with raloxifene that may play an important role in the selection of patients for preventive therapy. Raloxifene reduces breast cancer risk but increases thromboembolic events and hot flashes.

Parathyroid hormone — Parathyroid hormone (PTH) seems an unlikely candidate for the treatment of osteoporosis because of its well-described deleterious effect on bone. However, intermittent administration of recombinant human PTH (both full-length 1-84 or fragment 1-34) stimulates bone formation more than resorption and is effective for fracture reduction in women with osteoporosis. This topic is reviewed in detail elsewhere. PTH is also effective in men with osteoporosis.

Some of the newer medications which are used to treat bone mineral loss include

1. **Denosumab** -which is a monoclonal antibody directed against the receptor responsible for bone resorption. Osteoclasts are inhibited by this medication.
2. **Strontium ranelate** – it is drug which is being tried in animal models and it acts by decreasing bone resorption. Based upon changes in markers of bone formation and resorption in postmenopausal women with osteoporosis, it appears to have a modest antiresorptive effect, with little effect on bone formation

MATERIALS AND METHODS

STUDY DESIGN

This study was conducted on the patients admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Consecutive patients suffering from chronic liver disease admitted indoors in Department of Gastroenterology, DMC & H was enrolled for the study.

The patients were assesed for metabolic bone disease by measuring Sr Vit D3 level, Sr Parathyroid hormone, Sr Calcium, and DEXA Scan for osteoporosis and osteopenia at the time of enrolment and the one who found to be having metabolic bone disease is given treatment in the form of calcium, vit D3 and bisphosphonates, and evaluated again after 6 months for improvement of BMD.

SOURCES OF DATA

Consecutive patients suffering from Chronic liver disease admitted indoors in Department of Gastroenterology, DMC & H was enrolled for the study.

METHODS OF COLLECTION OF DATA

DATA COLLECTION

Confirmed and newly diagnosed cases of Chronic liver disease was enrolled.

Study design – Observational Study

Subjects: Patients with the diagnosis of chronic liver disease of all etiologies attending our department was included in this study. All the patients were explained in detail about the study, and an informed consent was obtained.

INCLUSION CRITERIA

1. Liver cirrhosis of all etiologies

EXCLUSION CRITERIA

1. Patients who were on calcium supplements and vitamin D

2. Patients on medications which affect bone mineral density

3. Postmenopausal women

4. Patients with coexistent chronic kidney disease

DURATION OF STUDY

The study period was from March 2019 to Oct 2019 with follow up period of 6 months till March 2020.

OUTCOME

Primary outcome

- To determine prevalence of metabolic bone disease in cirrhosis

Secondary outcome

- To determine the response of intervention on Bone mineral density
- To determine the severity of metabolic bone disease according to severity of liver disease.

Patients enrolled in the study were evaluated for the cause for liver disease.

Evaluation included

1. Hepatitis B
2. Hepatitis C
3. Wilson's disease
4. Alcoholic liver disease
5. Autoimmune hepatitis
6. Iron studies

Biochemical analysis

Blood for biochemical analysis was drawn from all patients enrolled in the study. After an overnight fast for 10 hours, blood for analysis was drawn in the morning. Biochemical analysis included liver function test, prothrombin time, renal function test, serum calcium, serum phosphosus, parathyroid hormone and vitamin D.

Liver function test, renal function test and prothrombin time analysis were done by automated method. Calcium estimation was done by arsenazo III method, and phosphorus was estimated by ammonium molybdate method. Parathyroid hormone and vitamin D were estimated by chemiluminescence immumunoassay (CIA).

BONE MINERAL DENSITY MEASUREMENT

All patients and controls included in the study were subjected to bone mineral density measurement by dual energy x-ray absorptiometry (DEXA). Dual energy x-ray absorptiometry was done by using HOLOGIC-QDR4500 machine.

Patients and controls were classified as having normal BMD or osteopenia or osteoporosis using the WHO criteria.

SEVERITY OF LIVER DISEASE

Severity assessment of the liver disease in patients with cirrhosis was done by Child Pugh score and Model for End Stage Liver Disease (MELD) scores.[14]

Figure 2 – HOLOGIC-QDR 4500 dual energy x-ray absorptiometry

STATISTICAL ANALYSIS

Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. A probability value (p value)less than 0.05 was considered statistically significant .All statistical calculations were done using (Statistical Package for the Social Science)SPSS 21version (SPSS Inc., Chicago, IL, USA)statistical program for Microsoft Windows.

OBSEVATIONS AND RESULTS

The present study was conducted in Dayanand Medical College and Hospital, Ludhiana in which 96 patients of cirrhosis were enrolled, to find out the presence of metabolic bone disease and the one who found to be having hepatic osteodystrophy in the form of low BMD is being treated and evaluated again after 6 months to see the response of therapy in the form of improvement in BMD on Dexa scan.

1. PATIENT PARAMETERS

1.1 AGE

Overall, the patient's age ranged from 31-72 years with mean age 52±8.71 years. The maximum number of patients 74 (77.1%) were in the age group of 40 to 60 years and lowest 8(8.3%) in less than 40 years.

Table 1. Age distribution of patients

Age group	No. of cases	Percentage
< 40	8	8.3%
41-60	74	77.1%
> 60	14	14.6%
Total	96	100.0%

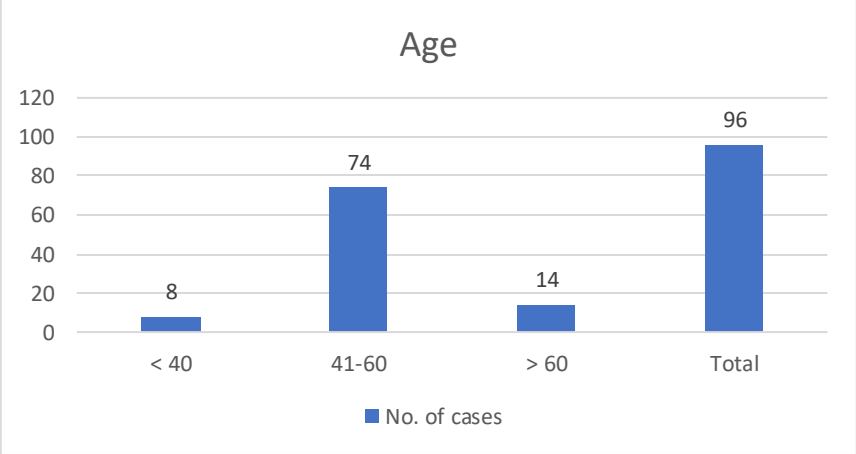

Figure 3. Age distribution of patients

1.2 SEX

In the study, there were 96 patients with cirrhosis, out of the which there was 80 male patients (83.3%) and 16 female patients (16.7%)

Table 2. Gender based distribution of patients

Gender	No. of cases	Percentage
F	16	16.7%
M	80	83.3%
Total	96	100.0%

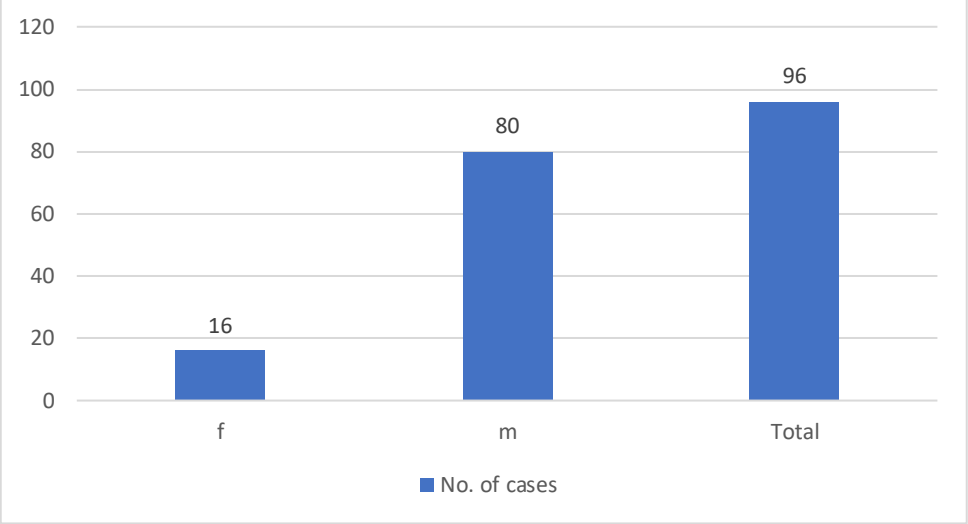

Figure 4. Gender based distribution of patients

2. AETIOLOGY OF CIRRHOSIS

In the study, there were 96 patients with cirrhosis, out of which alcohol is the most common etiology 53 patients(55.2%) followed by NASH 22 patients (22.9%), then hepatitis C 18 patients(18.8%) and hepatitis B 3 patients (3.1%).

Table 3. AETIOLOGY OF CIRRHOSIS

AETIOLOGY	NO. OF CASES	PERCENTAGE
ALCOHOL	53	55.2%
HBV	3	3.1%
HCV	18	18.8%
NASH	22	22.9%
TOTAL	96	100.0%

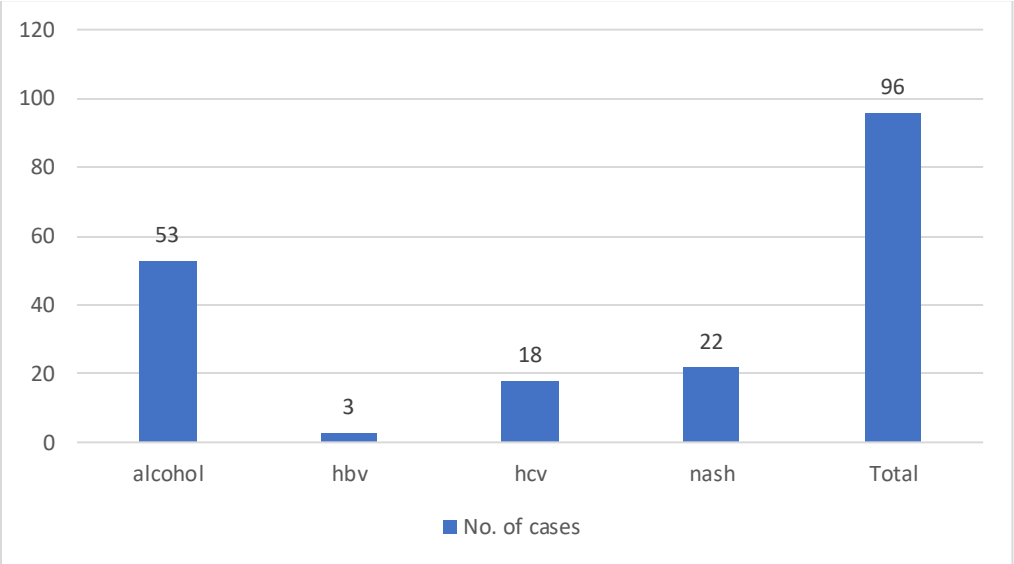

Figure 5. AETIOLOGY OF CIRRHOSIS

3. DURATION OF CIRRHOSIS

In the present study the maximum duration of cirrhosis is 68 months and minimum duration is 3 months with a mean duration of 27.7 ± 15.2 months. On the basis of this data cirrhotic patient were divided in 2 groups according to duration. 53 patients (55.2%) were of cirrhosis duration less than 30 months and 43 patients (44.8%) were in group more than 30 months.

Table 4. DURATION OF CIRRHOSIS

	N	Min.	Max.	Mean	SD
DURATION OF CIRRHOSIS(MONTHS)	96	3	68	27.72	15.172

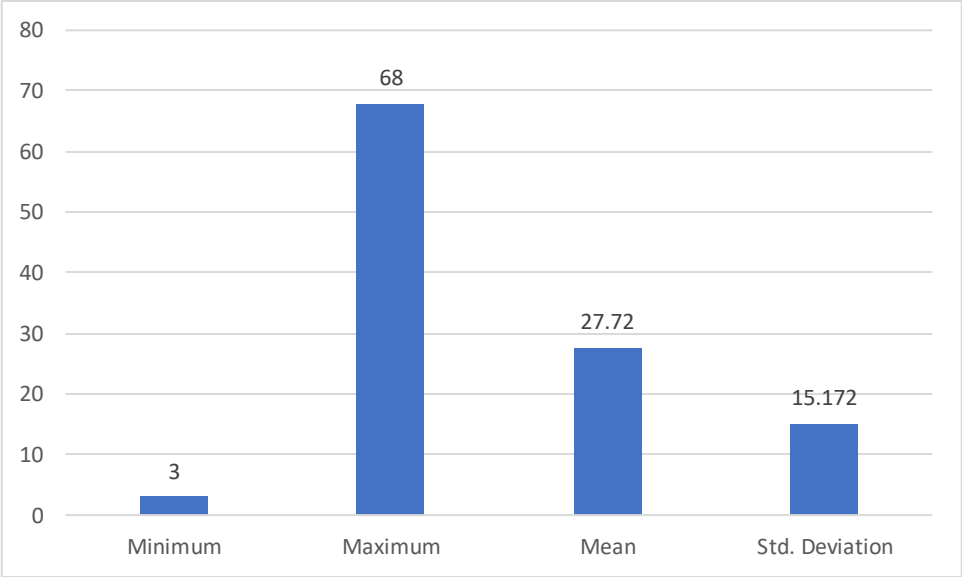

Figure 6. DURATION OF CIRRHOSIS

Table 5. GROUPS ON THE BASIS OF DURATION OF CIRRHOSIS

DURATION OF CIRRHOSIS	No. of cases	Percentage
< 30 months	53	55.2%
> 30 months	43	44.8%
Total	96	100.0%

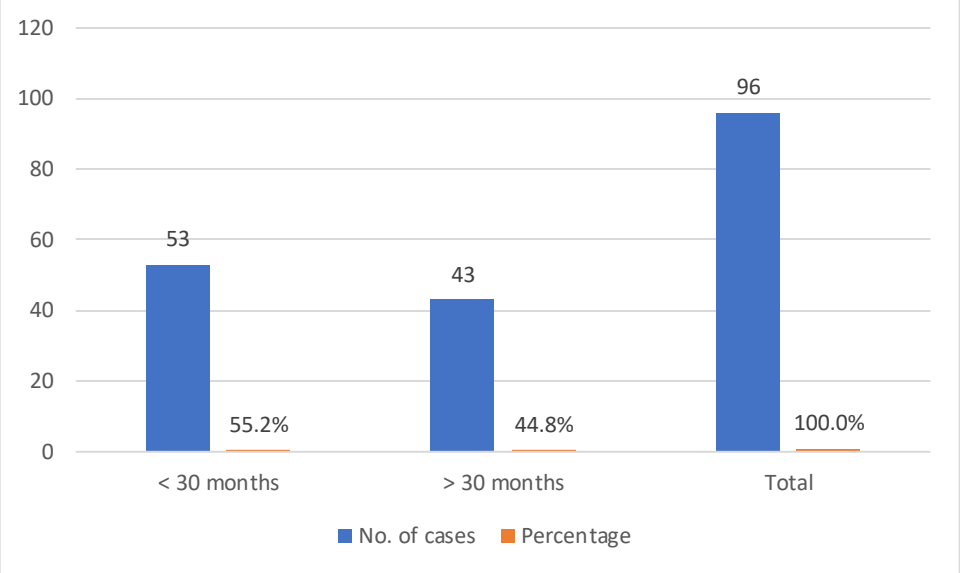

Figure 7. GROUPS ON THE BASIS OF DURATION OF CIRRHOSIS

4. CATEGORIZATION OF PATIENT ACCORDING TO CTP SCORE

In this study the patients are categorised on the basis of CTP score to assessed the severity of liver disease and it is found that out of 96 patient the majority of patients 42 (43.8%) fall into CTP score B, 32(33.3%) was in CTP class A and 22(22.9%) was in CTP class C which the most advanced stage of liver cirrhosis.

Table 6. CATEGORIZATION OF PATIENT ACCORDING TO CTP SCORE

CTP score	No. of cases	Percentage
A	32	33.3%
B	42	43.8%
C	22	22.9%
Total	96	100.0%

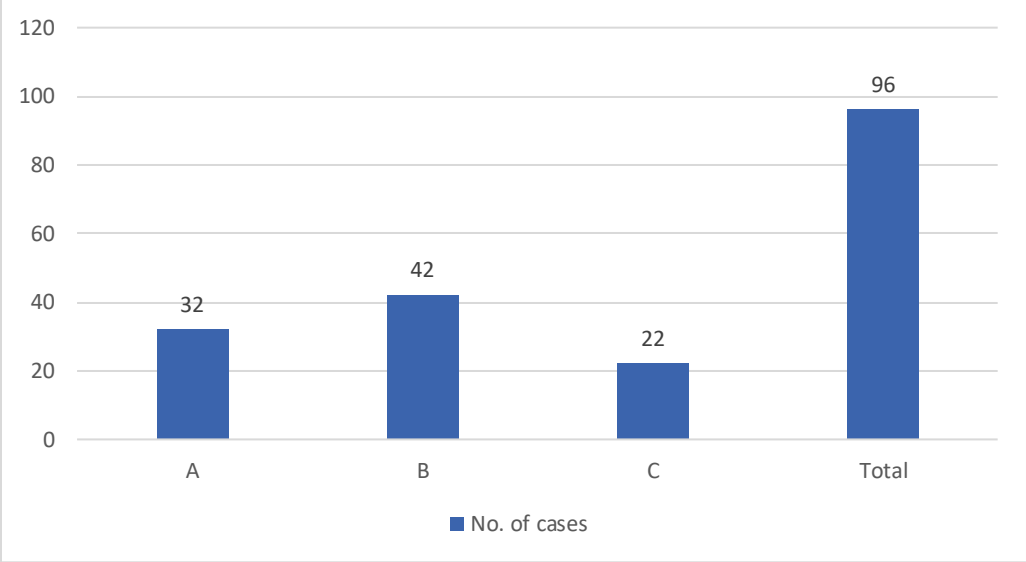

Figure 8. CATEGORIZATION OF PATIENT ACCORDING TO CTP SCORE

5. CALCIUM, PHOSPHORUS, VIT D3 AND PTH LEVELS IN CIRRHOSIS

The total no of patients having normal serum calcium is 84(87.5%), with a minimum value of 7 mg/dl and maximum value of 11 mg/dl and mean value of 8.6 ± 0.79 mg/dl and serum phosphorus level is 84 (87.5%), with a minimum value of 2.4 and maximum value 4.4 of with a mean value of 3.4± 0.53 while patient having low level is 12(12.5%) for both calcium and phosphorus, which is statistically not significant.

Table 7. CALCIUM AND PHOSPHORUS IN PATIENTS

Calcium	No. of cases	Percentage	phosphorus	No. of cases	Percentage
Normal	84	87.5%	Normal	84	87.5%
Low	12	12.5%	Low	12	12.5%
Total	96	100.0%	Total	96	100.0%

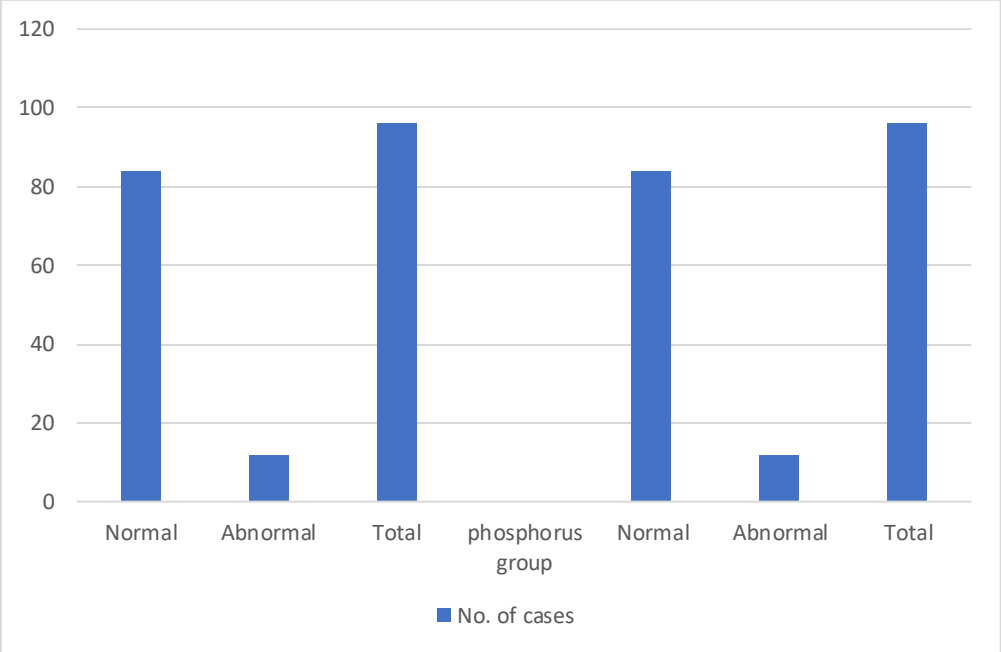

Figure 9. CALCIUM AND PHOSPHOROUS LEVELS IN CIRRHOSIS

5.1 In the present study the total no of patients having normal PTH level is 81(84.4%), with a minimum value of 4.6 and maximum value of 81.1 and mean value of 40.2 ± 14.7, the no of patient having high PTH is 15(15.6%). The patient having normal serum vitamin d3 level is 69(71.9%), with a minimum value of 8.7 and maximum value of 40 with a mean value of 24.5± 5.6 while patient having low level is 27(28.1%), which is statistically not significant.

Table 8. PARATHYROID HORMONE AND VITAMIN D3 LEVEL IN PATIENTS

PTH	No. of cases	Percentage	Vit D3	No. of cases	Percentage
Normal	81	84.4%	Normal	69	71.9%
High	15	15.6%	Low	27	28.1%
Total	96	100.0%	Total	96	100.0%

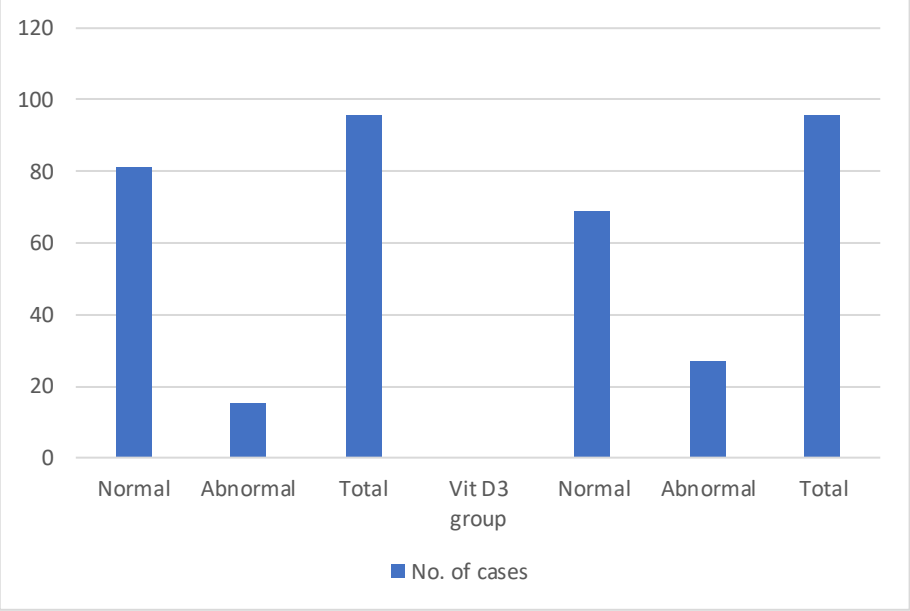

Figure 10. VIT D3 AND PTH LEVELS IN CIRRHOSIS

6. COMPLICATIONS OF CIRRHOSIS

In the present study out of 96 patients the total no of patients having ascites is 43(44.8%), HE is 29(30.2% and coagulopathy is 43(44.8%). In this study 27(28.1%) patients had no complications, 21(21.8%) patients had HE along with coagulopathy, 17(17.7%) patients had ascites with coagulopathy, 8(8.3%) patients had ascites along with HE while 6 (6.2%) patients had all the three complications.

Table 9. COMPLICATIONS OF CIRRHOSIS

COMPLICATION	NO. OF CASES	PERCENTAGE
ASCITES	43	44.8%
HE	29	30.2%
COAGULOPATHY	43	44.8%

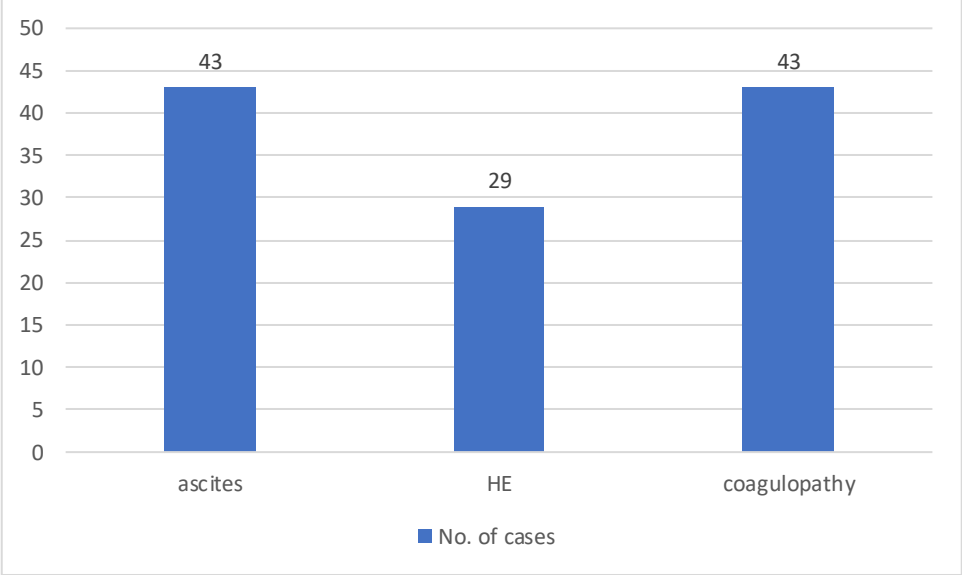

Figure 11. COMPLICATIONS OF CIRRHOSIS

7. DEXA SCAN FOR DETECTION OF BMD AT ENROLMENT

In the present study out of 96 patients the no of patients having normal BMD is 45(46.9%), and patient having osteopenia is also 45(46.9%), while 6(6.3%) patient were to be having osteoporosis.

Table 10. BMD OF PATIENTS ON ENROLMENT

BMD	No. of cases	Percentage
Normal	45	46.9%
Osteopenia	45	46.9%
Osteoporosis	6	6.3%
Total	96	100.0%

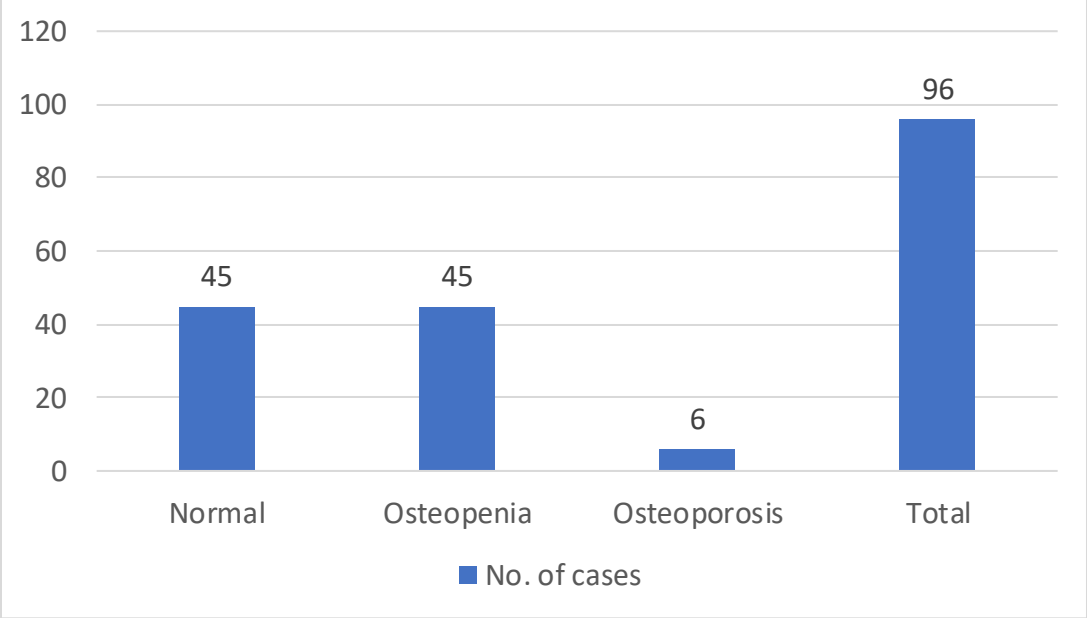

Figure 12. BMD OF PATIENTS ON ENROLMENT

8. BMD ACCORDING TO AGE OF PATIENTS

Out of the 51 patients with low BMD only 7 patients (13.7%) were from age group of less than 40 years. From the group 41 – 60 years out 74 patients (77%), 35 patients (47.2%) had low BMD. In the age group more than 60 years which consists total 14 patients (14.5%), out of which 9 patients (64.2%) had low BMD. The p value for this is 0.016 which is

statically significant and suggest that as age of patient increases the bone density decreases.

Table 11. BMD ACCORDING TO AGE OF PATIENTS

		BMD						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
Age group (years)	< 40	1	2.2%	7	15.6%	0	0.0%	8	12.23	0.016
	41-60	39	86.7%	32	71.1%	3	50.0%	74		
	> 60	5	11.1%	6	13.3%	3	50.0%	14		

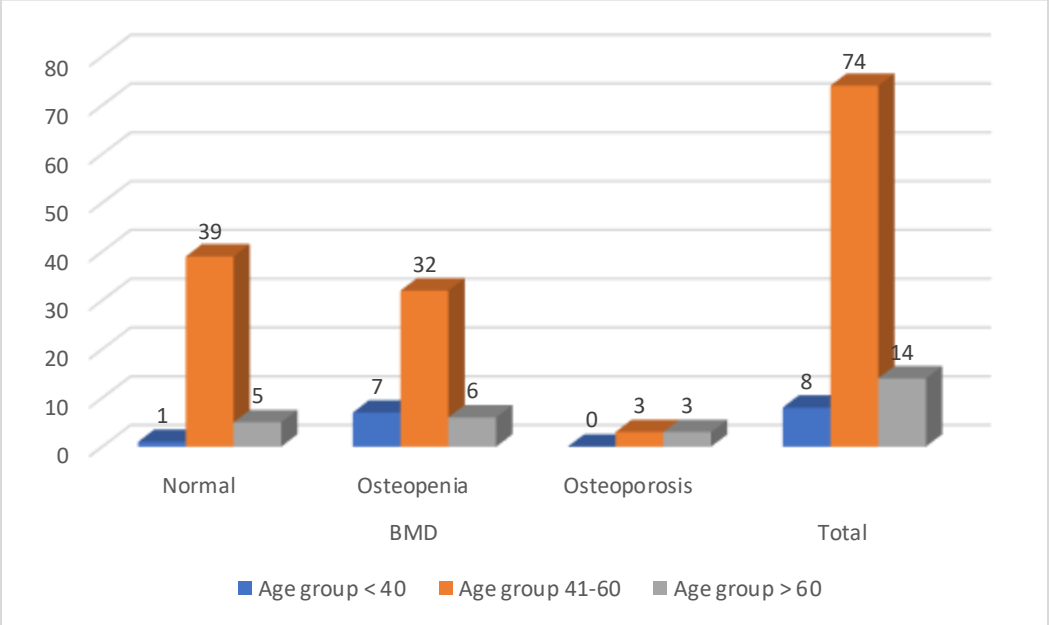

Figure 13. BMD ACCORDING TO AGE OF PATIENTS

9. BMD ACCORDING TO SEX OF PATIENTS

Out of the 16 female patients (16.6%) in this study 10 patients (62.5%) had low BMD, while out of 80 male patients (83.3%), 41 patients(51.2%) had low BMD. This suggest slightly high prevalence of hepatic osteodystrophy but due to small sample size it's not easy to establish the association. The p value is 0.278 which is statically not significant.

Table 12. BMD ACCORDING TO SEX OF PATIENTS

		BMD						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
SEX	F	6	13.3%	10	22.2%	0	0.0%	16	2.56	0.278
	M	39	86.7%	35	77.8%	6	100.0%	80		

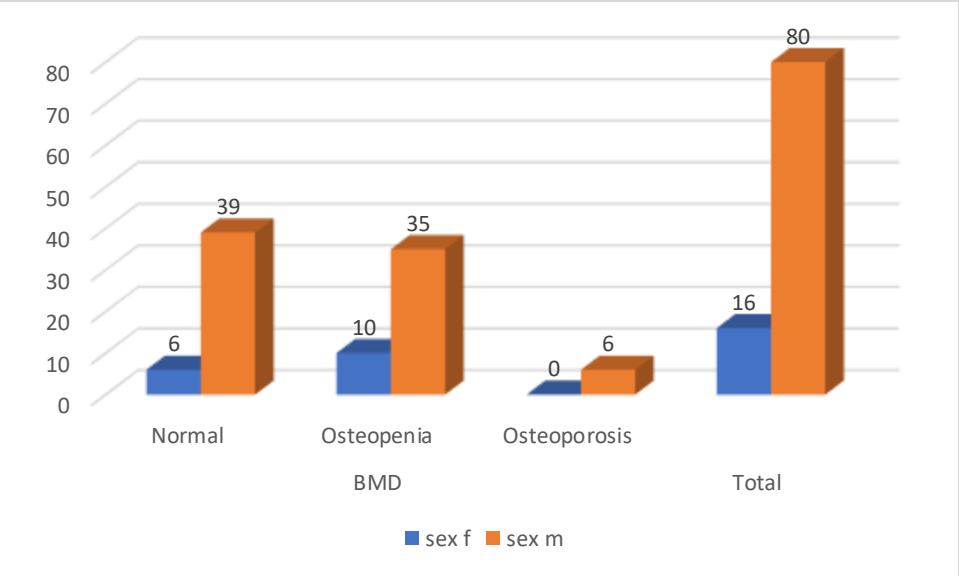

Figure 14. BMD ACCORDING TO SEX OF PATIENTS

10. ASSOCIATION OF CTP SCORE WITH DURATION OF CIRRHOSIS

In this study the patients are categorised on the basis of duration of cirrhosis and its association with the severity of liver disease according to CTP score. The patient were divided into two groups on the basis of duration of cirrhosis into less than 30 months or more than 30 months. The total no of patients in less than 30 months duration was 53(55.2%) and more than 30 months duration was 43(44.8%). Total no of patient in CTP class A was 32(33.96%) out of which 23(71.9%) was of duration less than 30 months while 9(28.1%) patient was of duration more than 30 months. In CTP class B there were 42(43.75%) patients which is equally divided both groups having 21(50%) patients each. In CTP class C the total no of patients were 22(22.9%) out which 13(59.1%) patients belong to duration more than 30 months while 9(40.9%) belongs to duration less than 30 months.

The p value for this association of duration of cirrhosis with severity of liver disease is 0.053 which not statistically significant but around borderline to be significant.

Table 13. ASSOCIATION OF CTP SCORE WITH DURATION OF CIRRHOSIS

		CTP score						Total	Chi-square value	p-value
		A		B		C				
Duration of cirrhosis	< 30 months	23	71.9 %	21	50.0 %	9	40.9 %	53	5.874	0.053
	> 30 months	9	28.1 %	21	50.0 %	13	59.1 %	43		

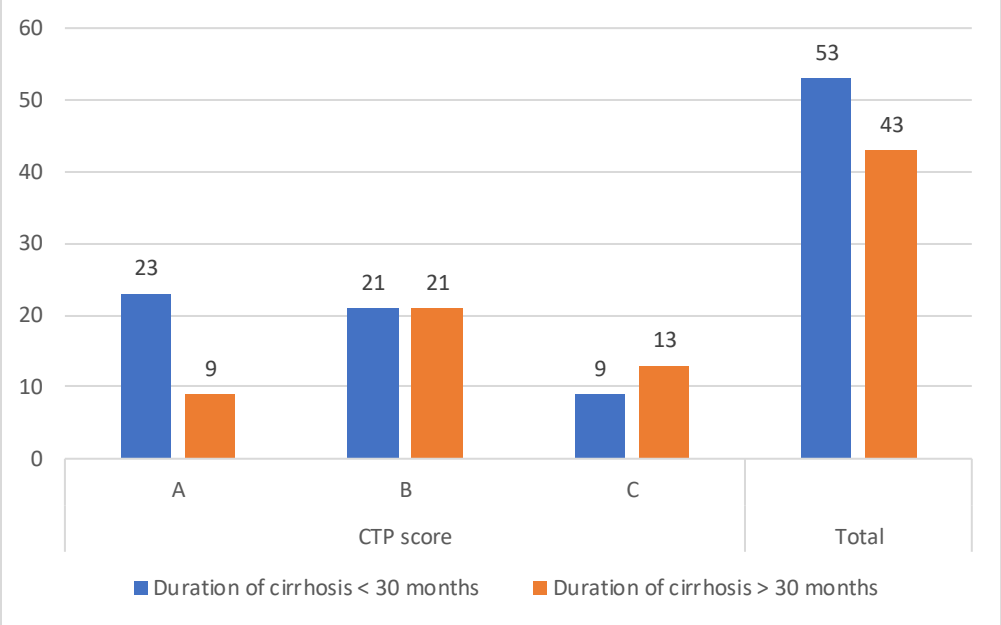

Figure 15. ASSOCIATION OF CTP SCORE WITH DURATION OF CIRRHOSIS

11. ASSOCIATION OF BMD WITH DURATION OF CIRRHOSIS

In the present as previously described the patient were divided in 2 groups on the basis of duration of cirrhosis less than and more than 30 months of cirrhosis, and also as described earlier there were total 45 patients who had normal BMD and 51 patients were found to be having low BMD. Out of 45(46.9%) patients with normal BMD 36(80%) were of cirrhosis less than 30 months while only 9(20%) were of more than 30 months duration. Of the 45(46.9%) patients with osteopenia 29(64.4%) were of group with cirrhosis of more than 30 months duration and only 16(35.6%) patients were of other group. 6(6.2%) patients who had osteoporosis, 5(83.3%) patients out of them were of duration more than 30 months and only 1(16.7%) was with cirrhosis duration less than 30 months.

The p value for this association of duration of cirrhosis with osteodystrophy is 0.0001 which is statistically significant and suggest there is more loss of BMD as the duration of disease increases.

Table 14. ASSOCIATION OF BMD WITH DURATION OF CIRRHOSIS

		BMD						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
Duration of cirrhosis	< 30 months	36	80.0%	16	35.6%	1	16.7%	53	21.817	0.00001
	> 30 months	9	20.0%	29	64.4%	5	83.3%	43		

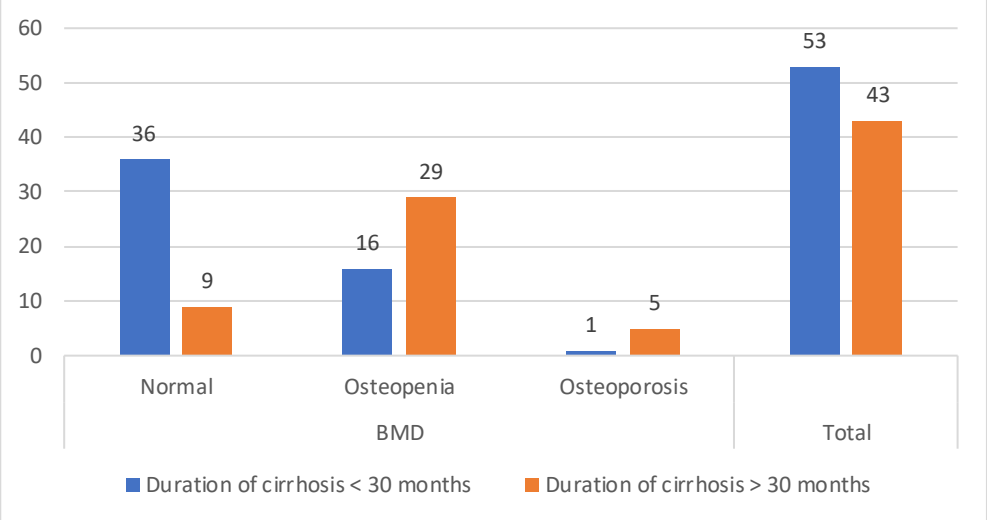

Figure 16. ASSOCIATION OF BMD WITH DURATION OF CIRRHOSIS

12. ASSOCIATION OF BMD WITH AETIOLOGY OF CIRRHOSIS

In the present study out of 53 (55.2%) patients of alcohol as etiology 22(48.9%) had normal BMD, while 25 (55.6%) patients had osteopenia while 6(100%) patient had osteoporosis, so total out of 53 patients 31(58.4%) had low BMD. Out of 22 (22.9%) patients of NASH as etiology 12(26.7%) had normal BMD while 10(22.2%) patients had osteopenia and no patient had osteoporosis, so 10(45.4%) patients out of 22 had osteopenia. Of the 18(18.75%) patients of Hep C as etiology 9(20%) had normal BMD ,and also 9(20%) patients had osteopenia and no patient had osteoporosis, which comes out to be 9(50%) had osteopenia. While hep B related cirrhosis patient 2(4.4%) had normal BMD and 1(2.2%) had osteopenia and none had osteoporosis, which suggest 1(33.3%) patient had osteopenia.

The p value for this association of etiology and low BMD is 0.432 which is statically not significant

Table 15. ASSOCIATION OF BMD WITH AETIOLOGY OF CIRRHOSIS

		BMD						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
AETIOLOY	ALCOHOL	22	48.9%	25	55.6%	6	100.0%	53	5.923	0.432
	HBV	2	4.4%	1	2.2%	0	0.0%	3		
	HCV	9	20.0%	9	20.0%	0	0.0%	18		
	NASH	12	26.7%	10	22.2%	0	0.0%	22		

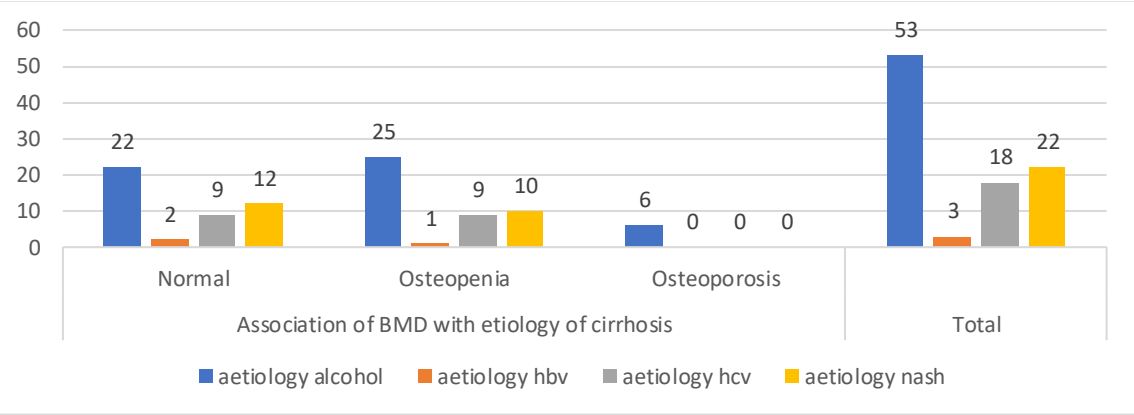

Figure 17. ASSOCIATION OF BMD WITH AETIOLOGY OF CIRRHOSIS

13. ASSOCIATION OF BMD WITH CTP SCORE

In the present study out of 32(33.3%) patients with CTP class A 21(65.6%) had normal BMD and 11(34.4%) had osteopenia and none had osteoporosis. Out of 42(43.7%) patients of CTP class B 18(42.9%) had normal BMD while 21(50%) had osteopenia and 3(7.1%) had osteoporosis, so 24(57.1%) patients out of 42 had low BMD. Out of 22(22.9%) patients of CTP class C 6(27.3%) had normal BMD while 13(59.1%) had osteopenia and 3(13.6%) had osteoporosis, so 16(72.7%) patients had low BMD

The p value for this association of CTP score and low BMD is 0.038 which is statically significant and suggest that hepatic osteodystrophy correlates with severity of liver disease.

Table 16. ASSOCIATION OF BMD WITH CTP SCORE

		CTP score						Total	Chi-square value	p-value
		A		B		C				
DEXA SCAN	Normal	21	65.6%	18	42.9%	6	27.3%	45	10.177	0.038
	Osteopenia	11	34.4%	21	50.0%	13	59.1%	45		
	Osteoporosis	0	0.0%	3	7.1%	3	13.6%	6		
Total		32	100.0%	42	100.0%	22	100.0%	96		

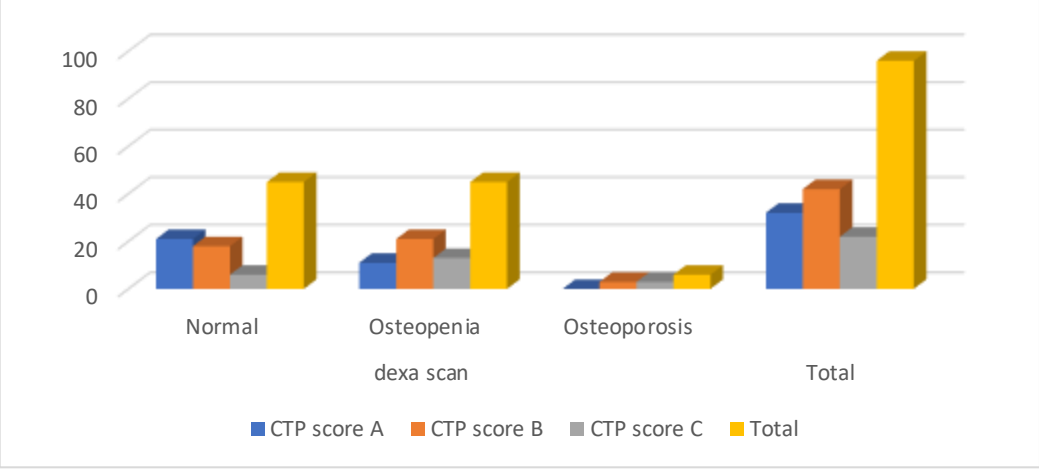

Figure 18. ASSOCIATION OF BMD WITH CTP SCORE

14. ASSOCIATION OF BMD WITH COMPLICATION OF CIRRHOSIS

Of the 43(44.8%) patients of 27(62.7%) patient had low BMD and 16(37.3%) patient had normal BMD. Similarly of the 43(44.8%) patient with coagulopathy 26(60.4%) patients had low BMD while 17(39.6%) had normal BMD. In 29(30.2%) patients with HE, 19(65.5%) patient were with low BMD while 10(34.5%) were with normal BMD. 27(28.1%) patients had no complications, 21(21.8%) patients had HE along with coagulopathy,17(17.7%) patients had ascites with coagulopathy,8(8.3%) patients had ascites along with HE while 6 (6.2%) patients had all the three complications.

Table 17. ASSOCIATION OF BMD WITH COMPLICATION OF CIRRHOSIS

		BMD						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
ASCITES	N	29	64.4%	21	46.7%	3	50.0%	53	2.946	0.229
	Y	16	35.6%	24	53.3%	3	50.0%	43		
HE	N	35	77.8%	28	62.2%	4	66.7%	67	2.612	0.271
	Y	10	22.2%	17	37.8%	2	33.3%	29		
COAGULOPATHY	N	28	62.2%	24	53.3%	1	16.7%	53	4.563	0.102
	Y	17	37.8%	21	46.7%	5	83.3%	43		

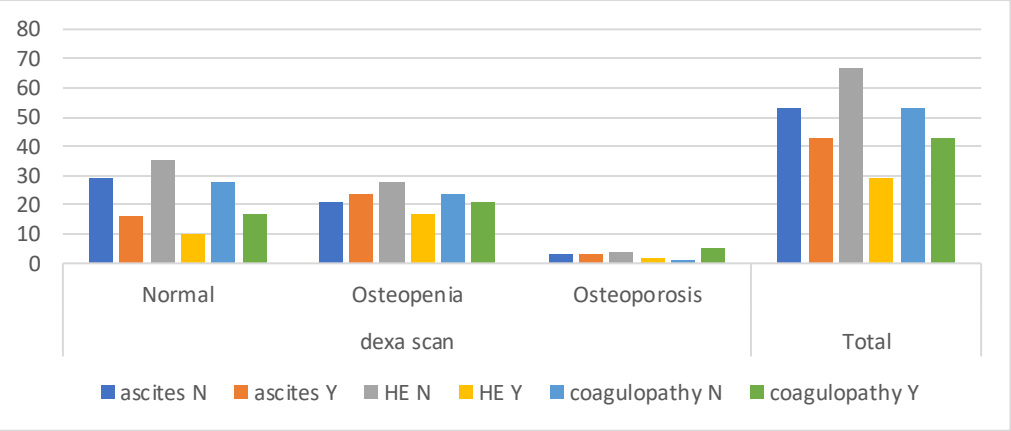

Figure 19.ASSOCIATION OF BMD WITH COMPLICATION OF CIRRHOSIS

13. ASSESMENT OF BMD AFTER THERAPY AT 6 MONTHS

Out of 45 (46.8%) patients of osteopenia after treatment with bisphosphonates, calcium and vit d supplements 23(51.1%) patients had shown improvement in BMD and had normal dexa scan after 6 months and out of 6(6.25%) patients of osteoporosis 3(50%) patients had come to osteopenia group. While 25 patients (49%) had not shown any improvement in BMD.

Table 18. ASSESMENT OF BMD AFTER THERAPY AT 6 MONTHS

		DEXA SCAN				Total
		Osteopenia		Osteoporosis		
BMD at 6 months	Normal	23	51.1%	0	0.0%	23
	Osteopenia	22	48.9%	3	50.0%	25
	Osteoporosis	0	0.0%	3	50.0%	3
Total		45	100.0%	6	100.0%	51

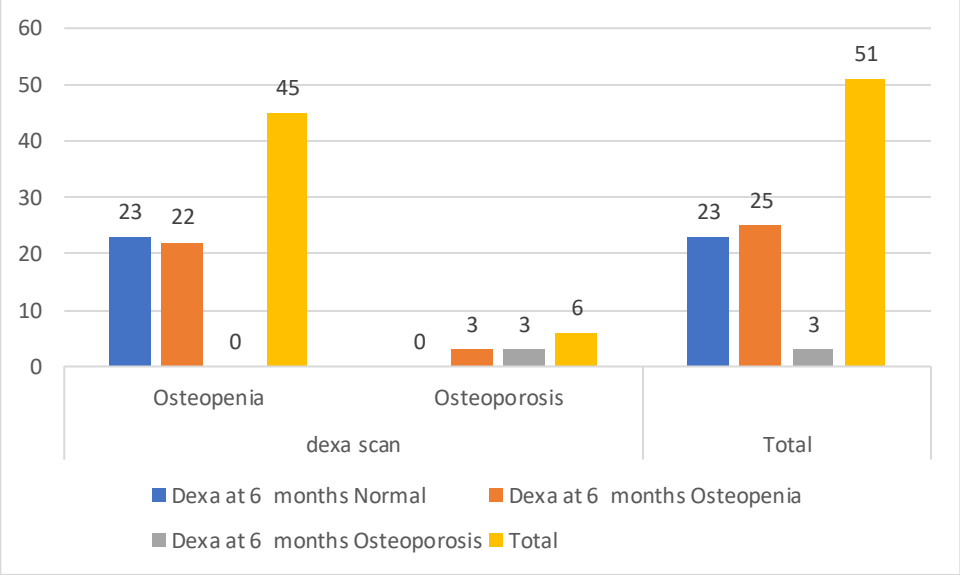

Figure 20. ASSESMENT OF BMD AFTER THERAPY AT 6 MONTHS

14. ASSESMENT OF BMD AFTER 6 MONTHS WITH DURATION OF CIRRHOSIS

Out 51 patients who had low BMD at enrolment 17(33.3%) were of cirrhosis duration less than 30 months, after treatment 14(82.3%) showed improvement in BMD which is statically significant (p value = 0.007). 34 patients (66.6%) of duration of cirrhosis more than 30 months who were found to be having low BMD, 13 patients (32.2%) had shown improvement in BMD while rest 21 patients (67.7%) had not shown any improvement in BMD.

Table 19. ASSESMENT OF BMD AFTER 6 MONTHS WITH DURATION OF CIRRHOSIS

		BMD at 6 months						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
DURATION OF CIRRHOSIS	< 30 months	13	56.5%	4	16.7%	0	0.0%	17	9.958	0.007
	> 30 months	11	43.5%	20	83.3%	3	100.0%	34		

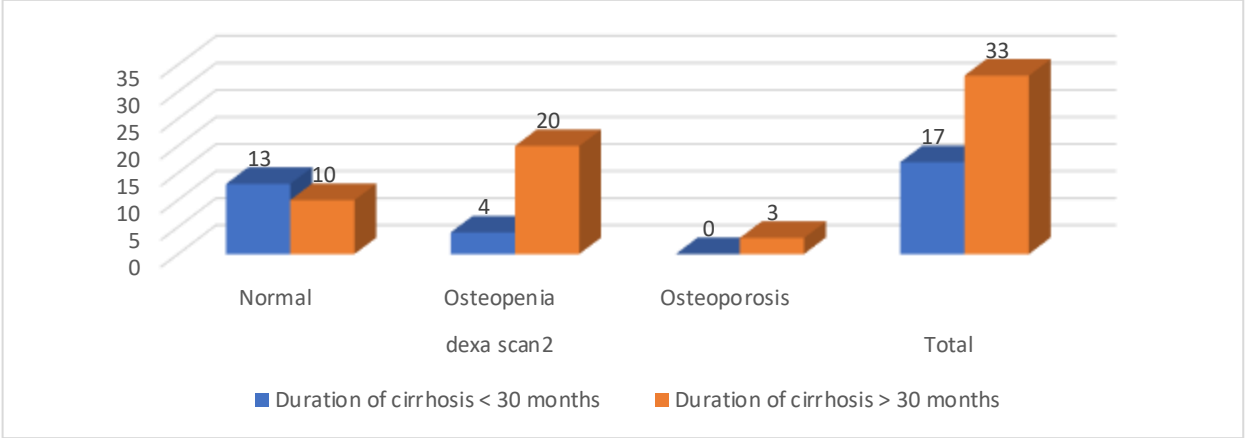

Figure 21.ASSESMENT OF BMD AFTER 6 MONTHS WITH DURATION OF CIRRHOSIS

15. BMD AFTER 6 MONTHS WITH AETIOLOGY OF CIRRHOSIS

Out of 53(55.2%) patients of alcohol as etiology 31(58.4%) patient had low BMD, on repeat dexa scan at 6 months 17(54.8%) had shown improvement in BMD. In NASH associated cirrhosis out of 22 patients 10(22.2%) patients had low BMD in the form of osteopenia ,on repeat Dexa scan at 6 months 4 patients (40%) had normal BMD while 6 (60%) patients didn't shown any improvement in BMD. In 9 patients (50%) of Hep C related cirrhosis who had low BMD on repeat dexa scan at 6 months 5(55.5%) had shown improvement in BMD and had normal dexa scan while 4 patients (44.5%) had not shown any improvement. Only 1 patient of Hep B related cirrhosis had osteopenia and she didn't show any improvement on repeat scan.

The p value for this association is 0.711 which is statically not significant.

Table 20. BMD AFTER 6 MONTHS WITH AETIOLOGY OF CIRRHOSIS

		BMD at 6 months						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
AETIOLOGY	ALCOHOL	14	60.9%	13	54.2%	3	100.0%	30	3.743	0.711
	HBV	0	0.0%	1	4.2%	0	0.0%	1		
	HCV	5	21.7%	4	16.7%	0	0.0%	9		
	NASH	4	17.4%	6	25.0%	0	0.0%	10		

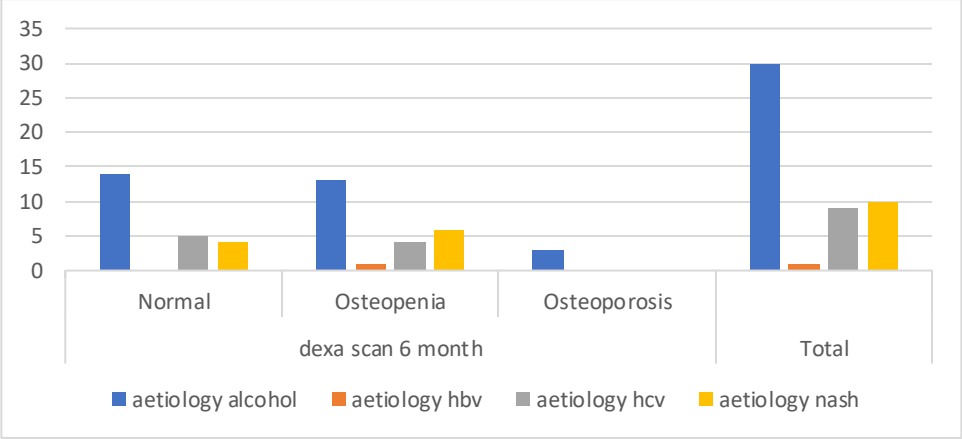

Figure 22.BMD AFTER 6 MONTHS WITH AETIOLOGY OF CIRRHOSIS

16. BMD AFTER 6 MONTHS WITH CTP SCORE CORRELATION

Of the 11(34.3%) patients out of 32(33.3%)patients of CTP class A who had low BMD at presentation, after treatment and repeat dexa scan at 6 months 6 (54.5%) patients had normal BMD and 5 (45.5%) patients had no response. 24(57.1%) patients out of 42(43.75%) patients of CTP class B who had low BMD 12 patients(50%) had shown improvement in BMD while 12 patients (50%) had no response. In CTP class C 16(72.7%) patients out of 22 patients had low BMD, after 6 months 5 patients (31.2%) had normal BMD while 2 (12.5%) patients had improvement in BMD from osteoporosis to osteopenia. So total 7 patients (43.7%) had shown improved BMD after 6 months of therapy.

The p value for this association is 0.538 which is statically not significant but can be clinically useful if duration of follow up increased.

Table 21. BMD AFTER 6 MONTHS WITH CTP SCORE CORRELATION

		BMD after 6 month						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
CTP score	A	6	26.1%	5	16.7%	0	0.0%	11	3.12	0.538
	B	12	52.2%	10	41.7%	2	66.7%	24		
	C	5	21.7%	10	41.7%	1	33.3%	16		
Total		23	100.0%	24	100.0%	3	100.0%	50		

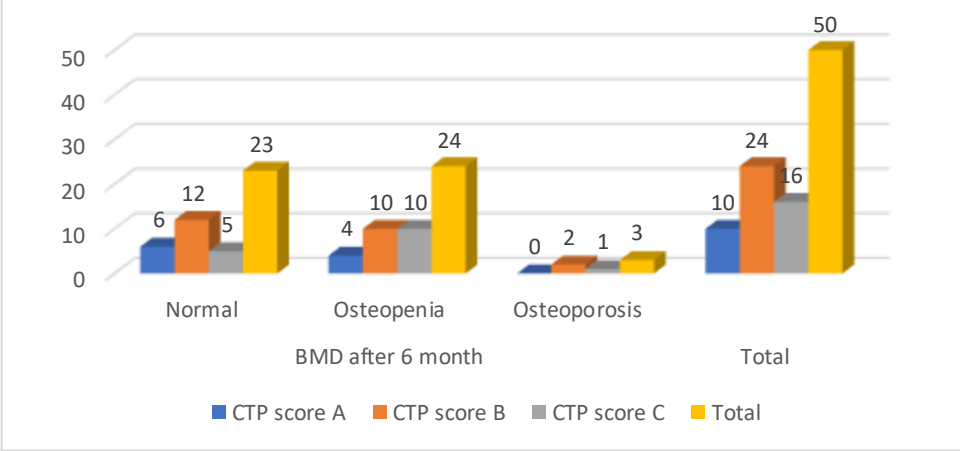

Figure 23.BMD AFTER 6 MONTHS WITH CTP SCORE CORRELATION

17. BMD AFTER 6 MONTHS WITH COMPLICATIONS OF CIRRHOSIS CORRELATION

Of the 27(62.7%) patients of ascites with low BMD 12 patients (44.4%) had improvement in there BMD after 6 months. Similarly of the 26 (60.4%) patient of coagulopathy who had low BMD 8 (30.7%) had normal BMD after 6 months of therapy, In 19(30.2%) patients of low BMD with HE, 10(52.6%) patient had improvement in BMD after 6 months. The p value of this correlation is not significant for any complications.

Table 22. BMD AFTER 6 MONTHS WITH COMPLICATIONS OF CIRRHOSIS CORRELATION

		BMD after 6 Months						Total	Chi-square value	p-value
		Normal		Osteopenia		Osteoporosis				
ASCITES	N	11	47.8%	10	41.7%	2	66.7%	23	0.728	0.695
	Y	12	52.2%	14	58.3%	1	33.3%	27		
HE	N	13	56.5%	15	62.5%	3	100.0%	31	2.134	0.344
	Y	10	43.5%	9	37.5%	0	0.0%	19		
COAGULOPATHY	N	15	65.2%	10	41.7%	0	0.0%	25	5.797	0.055
	Y	8	34.8%	14	58.3%	3	100.0%	25		
Total		23	100.0%	24	100.0%	3	100.0%	96		

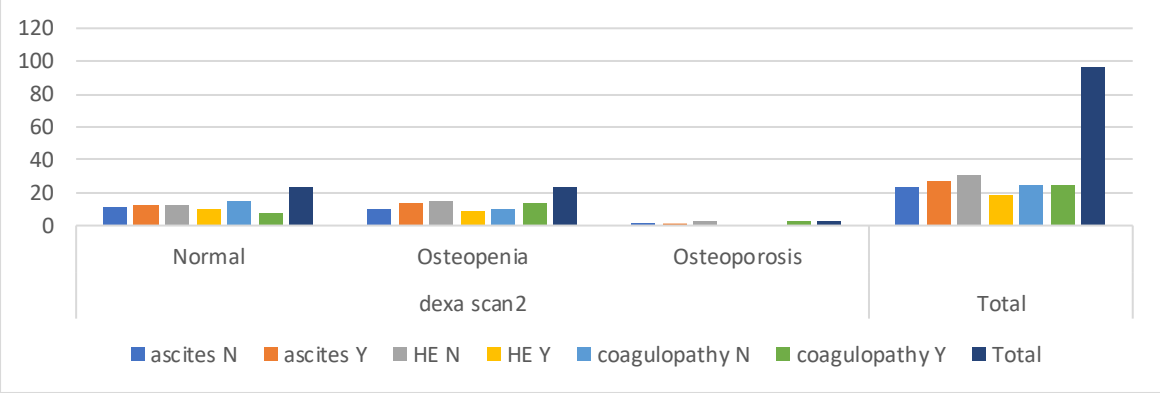

Figure 24.BMD AFTER 6 MONTHS WITH COMPLICATIONS OF CIRRHOSIS CORRELATION

DISSCUSSION

Cirrhosis (Chronic liver disease) is a significant cause for morbidity and mortality worldwide and may lead to various complications, such as liver failure, portal hypertension, hepatorenal syndrome, ascites, encephalopathy and oesophageal variceal haemorrhage. Chronic liver disease is also a risk factor for osteoporosis, osteopenia and bone fractures.[2] Hepatic osteodystrophy is a term used to describe metabolic bone diseases, such as osteopenia, osteoporosis and osteomalacia, seen at various degrees due to chronic liver disease.[3] While osteomalacia is a rare condition accompanying chronic liver disease,[4] osteoporosis is more common (11–55%).[3–5]

Hepatic osteodystrophy is a bone disease of multifactorial origin associated with chronic liver disease.[7] Cholestatic liver disease has higher incidence of hepatic osteodystrophy than non cholestatic liver disease, but BMD loss is present in all aetiologies of cirrhosis[8].

Metabolic bone disease (hepatic osteodystrophy) is one the metabolic complication associated with cirrhosis. With improvement in management of chronic liver disease patients and with more number of liver transplantation being done these days, it is imperative to maintain a good quality of life in these patients[29,30]. One of the factors which cause a decrease in quality of life, in patients with cirrhosis is decrease in bone mineral density, by increasing the risk of fragile fractures. But most of the patients with metabolic bone disease are not recognized, as there is no proper screening done in these patients.

In present study, there was a significant number of cirrhotic patients who had decreased bone mineral density. In a study from India, Joe George et al[31] has reported 68% prevalence of low bone mineral density in chronic liver disease patients. Another study from Chandigarh, Choudhary et. al[32] has shown the prevalence of low bone mineral density in non cholestatic chronic liver disease to be around 80%. In this study, we had 46.9% cirrhotic patient to have osteopenia and 6.3% patients to have osteoporosis while 46.8% patient had normal BMD.

Lumbar spine and femur neck are the common sites to measure bone mineral density, as it is composed of more trabecular bone. But in patients with cirrhosis, due the presence of ascites measuring bone mineral density in the lumbar spine is controversial. Guanabans.N et al[24] has shown that measuring bone mineral density in the lumbar spine is highly inaccurate giving false positive reports. In our study we had taken the femur neck as site of measurement to avoid false positive reports.

In present study, the common aetiology of cirrhosis was alcohol in 53 patients (55.2%), NASH in 22 patients (22.9%), HCV in18 patients (18.8%) and HBV in 3 patients (3.1%). Among patients who had low bone mineral density aetiology was Alcohol in 31 patients (60.7%) [33], followed by NASH 10 patients (19.6%), then HCV 9 patients (17.6%) and Hep B 1 patient (1.9%). Study by Choudhary et al[32] has shown the aetiology of cirrhosis to be alcohol in 58.2% and viral in 41.1%. In present study aetiology of cirrhosis has no correlation with improvement in bone mineral density after 6 months, all patients had same response to therapy irrespective of any aetiology

In present study the Severity of cirrhosis showed significant correlation with the bone mineral loss. Patients with CTP class A only 11 (34%) had low bone mineral density and no patient had osteoporosis. 24 patients (57.1%) in the study with CTP class B had low bone mineral density and 16 patients (72.7%) with CTP class C had low bone mineral density (P value – 0.038), which is statistically significant and suggests that hepatic osteodystrophy correlates with the severity of liver disease. In a study by sokhi RP et al[34] similar results were achieved which suggest that severity of liver disease is directly correlated with loss of bone mineral density, but studies by Ashraful et al[35] and Chen et al.[36] has shown no relation between the severity of liver disease and bone mineral loss. On repeat DEXA Scan after 6 months there was no significant correlation between improvement in bone mineral density and severity of liver disease in our study. So, this required further study to establish the association of low bone mineral density and severity of liver disease.

In current study the duration of cirrhosis also showed significant correlation with low bone mineral density. 17 patients (32%) had low bone mineral density in group with cirrhosis duration less than 30 months, while 34 patients (79%) in cirrhosis duration more than 30 months had low bone mineral density (p value=0.0001) which is statically significant. Out of the 17 patients of cirrhosis duration 14 patients (82.3%) had improvement in bone mineral density on repeat DEXA scan at 6 months (p value =0.007) which is statically significant , while out of 34 patients of cirrhosis duration more than 30 months only 13 patients (38.2%) had shown improvement in bone mineral density. So this result suggest that hepatic osteodystrophy increases with increase duration of cirrhosis and also response to intervention is more in early stages of cirrhosis and hence it is better to screen for low bone mineral density early and treat as early as possible. In a study from Pakistan by Hozaifa Iqbal et al [37] similar results were obtained where loss of bone mineral density was directly correlated with duration of cirrhosis and was more in patients with cirrhosis duration of more than 3 years.

In present study to assess the response of pharmacological intervention on low bone mineral density we have supplemented the patient of low bone mineral density with calcium (1000 mg/day), vitamin D (800 IU/day) and bisphosphonate (alendronate, zolendronic acid).[38-41] Out of 51 patients (53.1%) of low bone mineral density 26 patients (51%) showed improvement in bone mineral density after follow up at 6 months. In a study from Zein CO et al in 2005 also showed significant improvement in BMD at 1 year in patients of Primary Biliary Cirrhosis but our study differs from that study in in design, we have followed the patient at 6 months as compared to 1 year and our study predominantly consists of male patients (83.3%) and cirrhosis of all aetiologies, while study from Zein co et al consists of predominantly female patients only.[42] Results similar to our study were also observed in a study by Crawford BA et al [40] in 2006 from Australia in patients of post liver transplant which showed significant improvement in BMD at 1 year, but in that study, there is improvement in liver function post-transplant. In view of limited studies,

we may need larger studies to associate the role of bisphosphonates as a therapeutic drug for increasing BMD and prevent fractures in cirrhosis.

In present study, the majority of patients 74 (77%) were from the age group 41 to 60 years out of which 35 patients (47.2%) had low bone mineral density, while out of 14 patients of age group more than 60 years 9 patients (64.2%) had low bone mineral density (p value = 0.016) which is statically significant and suggest that as age of patient increases there is much more loss of bone mineral density. In a similar study from japan by Takeo Toshima et al[43] and Figueiredo FAF et al [44] from brazil in cirrhosis of liver it was shown that increasing age correlate with low bone mineral density. Very few studies till date has been done regarding this, so this needs further study.

In present study no significant correlation was found between serum levels of calcium, phosphorous, vitamin D3, parathyroid hormone levels and bone mineral density. In our study only 27% patients had low serum vitamin D3. In a similar study from PGI Chandigarh by Choudhary et al[32] it was found that vitamin D deficiency was present in only 38% patients and also there was significant correlation of hepatic osteodystrophy and vitamin D, calcium, PTH and phosphorous levels.

SUMMARY AND CONCLUSION

The present study was conducted on the patients of chronic liver disease admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

96 patients were assesed for metabolic bone disease by measuring Sr Vit D3 level, Sr Parathyroid hormone, Sr Calcium, and DEXA Scan for osteoporosis and osteopenia at the time of enrolment and the 51 patients out of them found to be having metabolic bone disease is given treatment in the form of calcium, vit D3 and bisphosphonates, and evaluated again after 6 months for improvement of BMD.

Inference from this study include

1. The mean age of patients was 52±8.71 years, and the maximum number of patients 74 (77.1%) were in the age group of 40 to 60 years
2. The prevalence of Hepatic osteodystrophy was more than 50% and it is common in people with chronic liver disease.
3. There was a male predominance (80%) noted in our study.
4. In present study as the age of patient increases there is much more loss of bone mineral density.
5. The most common aetiology for cirrhosis of liver in our study was alcohol (55.2%) and there was no correlation of aetiology of cirrhosis with bone mineral loss.
6. Longer duration of cirrhosis (> 30 months) in patients was significantly related to the bone mineral loss.
7. Severity of the liver disease (CTP C) was significantly related to the bone mineral loss. As liver disease become more severe there is more loss of bone mineral density.
8. There was no correlation of vitamin D, calcium, parathyroid hormone levels with bone mineral loss.
9. In present study there is improvement in bone mineral density in patient of hepatic osteodystrophy with bisphosphonates, calcium and vitamin D supplements after 6 months.

10. In this study it is also evident that if hepatic osteodystrophy detected early and treated it shows much more improvement with therapy as compared to hepatic osteodystrophy of long duration.
11. In view of high prevalence of metabolic bone disease in patients with chronic liver disease, screening for bone mineral loss with DEXA scan should be done, initially at diagnosis and then regularly.

Conclusion

Hepatic osteodystrophy is a well known metabolic complication of chronic liver disease, still regular surveillance for metabolic bone disease is not done in patients of chronic liver disease.

In our study of 96 patients of cirrhosis (chronic liver disease), the prevalence of metabolic bone disease is high (>50%) and its prevalence increases as the severity and duration of liver disease increases, it is also evident from the study that hepatic osteodystrophy is more common in patients of old age but this need to be studied further due to other confounding factors. In this study it is also evident that earlier the metabolic bone disease detected and treated the better is outcome and prevention of fractures.

So in view of high prevalence of metabolic bone disease in patients with chronic liver disease, screening for bone mineral loss with DEXA scan should be done, initially at diagnosis and then regularly and patients with metabolic bone disease should be treated early.

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KEY TO MASTER CHART

NASH-	Non-alcoholic steato hepatitis
HCV-	Hepatitis C virus
HBV-	Hepatitis B virus
CTP -	Child Turcotte Pugh
SGOT -	Serum Glutamic oxaloacetic Transaminase
SGPT -	Serum Glutamic Pyruvate Transaminase
INR -	International Normalized Ratio
ALP -	Alkaline Phosphatase
HE -	Hepatic Encephalopathy
PTH -	Parathyroid hormone
MELD -	Model for end liver disease
DEXA -	Dual energy X ray absorptiometry
Y -	Yes
N -	No

Sr. No.	name of the patient	age	sex	diagnosis	aetiology	T.Bilirubin	ALP	SGOT	SGPT	albumin	INR	calcium	phosphorus	PTH	vitamin D3	dexa scan	Dexa at 6	CTP score	MELD	CTP score	Fibroscan	duration of cirrhosis	ascites	HE	coagulopathy
1	SCD	42	m	cirrhosis	alcohol	4.2	134	42	38	2.5	2.0	9.8	2.7	31.3	40	osteopenia	Osteopenia		22	C	-	68 months	Y	Y	Y
2	S	46	f	cirrhosis	nash	1.2	98	68	57	3.4	1.4	8.4	3.9	38.6	20.9	osteopenia	normal		10	A	F4	5 months	N	N	N
3	SR	48	f	cirrhosis	hcv	0.9	142	59	63	3.1	1.5	7.4	4.4	52.5	25.4	osteopenia	osteopenia		14	B	-	34 months	N	Y	N
4	GS	62	m	cirrhosis	alcohol	2.3	98	75	48	3.1	1.7	8.1	4.1	23.4	22.39	osteoporosis	osteopenia		18	C	-	35 months	N	Y	Y
5	VS	58	m	cirrhosis	alcohol	2.3	163	81	72	3.1	1.8	7.4	2.7	47.2	30.33	osteopenia	osteopenia		16	B	-	46 months	Y	N	Y
6	BRS	47	m	cirrhosis	hcv	1.6	198	40	38	3.6	1.4	7.9	4.4	21.5	22.47	normal	-		13	B	-	25 months	N	N	N
7	JS	45	m	cirrhosis	alcohol	3.9	105	54	46	2.9	1.8	9.6	2.8	4.6	8.71	osteopenia	osteopenia		20	C	-	47 months	Y	Y	Y
8	JK	59	f	cirrhosis	nash	0.9	113	74	84	3.7	1.3	8.2	3.7	55.4	20.07	normal	-		9	A	-	22 months	N	N	N
9	VK	72	m	cirrhosis	nash	0.8	98	32	43	3.5	1.1	8.2	3.9	32.3	25.92	Normal	-		9	A	-	12 months	N	N	N
10	RK	60	m	cirrhosis	alcohol	1.4	179	78	53	3.2	1.7	7.9	3.3	35.8	21.4	osteopenia	normal		16	B	-	24 months	N	Y	Y
11	NK	47	m	cirrhosis	nash	1.2	99	45	62	3.5	1.4	7.9	3.4	39.1	27.42	osteopenia	osteopenia		10	A	F4	32 months	N	N	N
12	RS	47	m	cirrhosis	alcohol	1.5	102	32	41	3.1	1.6	8.5	4	33.6	28.2	osteoporosis	osteoporosis		14	B	-	60 months	N	N	Y
13	KG	59	m	cirrhosis	alcohol	0.8	94	38	47	3.6	1.5	8.1	3.9	68.7	19.2	Normal	-		9	A	F4	5months	N	N	N
14	SS	45	m	cirrhosis	alcohol	2.2	116	102	93	3.4	1.6	8.4	3.6	33	20.8	osteopenia	normal		17	B	-	56months	Y	Y	Y
15	CS	65	m	cirrhosis	alcohol	1.1	147	82	63	3.3	1.5	8.8	4.1	38.5	22.5	Normal	-		14	A	-	3months	N	N	N
16	MK	60	f	cirrhosis	hcv related	1.2	134	58	64	3.4	1.4	8.6	3.4	28.2	35.6	osteopenia	osteopenia		9	A	F4	22 months	N	N	N
17	SS	45	m	cirrhosis	alcohol	3.9	172	67	52	3.1	1.8	7.8	3.1	40.2	33.8	osteopenia	normal		20	C	-	13 months	Y	N	Y
18	AS	46	m	cirrhosis	alcohol	2.1	181	73	53	3.1	1.8	7.9	2.7	81.1	22.7	osteopenia	osteopenia		17	C	-	48 months	N	Y	Y
19	RS	57	m	cirrhosis	alcohol	1.5	109	59	68	3.1	1.6	7.8	3.2	37.1	20.5	osteopenia	-		-	A	-	44 months	N	N	Y
20	RS	48	m	cirrhosis	alcohol	1.3	112	62	59	3.5	1.3	6.9	3.1	33.8	23.5	Normal	-		13	A	F4	5months	N	N	N
21	TD	49	f	cirrhosis	nash	0.8	96	47	61	3.6	1.4	7.8	2.9	52.3	25.5	osteopenia	normal		10	B	-	30 months	Y	N	N
22	IS	62	m	cirrhosis	alcohol	0.9	165	67	62	3.5	1.3	6.6	3.5	40	18.9	osteopenia	normal		11	B	-	48 months	Y	N	N
23	CP	55	f	cirrhosis	nash	0.7	113	54	39	3.3	1	7.2	3.7	32.3	23.4	Normal	-		9	A	F4	6months	N	N	N
24	JR	53	m	cirrhosis	nash	1.1	121	92	87	3.1	1.4	6.8	2.9	29.9	20.5	osteopenia	osteopenia		11	B	-	40 months	Y	N	N
25	A	35	f	cirrhosis	hcv related	1.1	132	45	49	3.6	1.5	8.7	2.4	66.8	28.6	osteopenia	normal		11	A	F4	7 months	N	N	N
26	SB	50	m	cirrhosis	alcohol	0.8	99	94	71	3.2	1.3	7.9	3.9	45.9	23.4	osteoporosis	osteopenia		12	B	-	28 months	Y	N	N
27	KG	50	m	cirrhosis	alcohol	0.9	124	37	41	3.4	1.3	8.1	3.3	28.7	27	osteopenia	normal		14	B	-	30 months	N	Y	N
28	RM	36	M	cirrhosis	alcohol	1.8	156	38	32	3.1	1.6	7.8	2.9	33.7	25.6	osteopenia	osteopenia		16	B	-	24 months	Y	N	Y
29	SS	46	m	cirrhosis	alcohol	3.4	118	96	50	2.8	1.9	7.8	3.1	42	20.8	osteopenia	osteopenia		18	C	-	40 months	N	Y	Y
30	DS	53	m	cirrhosis	Hcv related	1.8	153	112	97	3.1	2.4	8.3	3.2	54.8	29.8	osteopenia	normal		18	B	-	54 months	N	Y	Y
31	VJ	50	m	cirrhosis	nash	2.1	188	65	71	2.9	1.5	7.7	3.9	34.9	22.8	osteopenia	normal		14	B	-	47 months	Y	N	N
32	TL	58	m	cirrhosis	alcohol	1.6	145	42	36	3.5	1.5	8.1	2.9	48.4	27.5	osteopenia	Normal		13	A	F4	20 months	N	N	N
33	AS	65	m	cirrhosis	alcohol	5.2	134	42	38	2.1	2.2	9.8	2.7	31.3	40	normal	-		27	C	-	20 months	Y	N	Y
34	KK	62	f	cirrhosis	nash	1.2	98	68	57	3.4	1.4	8.4	3.9	38.6	20.9	osteopenia	normal		10	A	-	24 months	N	N	N
35	TD	55	f	cirrhosis	nash	0.9	142	59	63	3.1	1.5	7.4	4.4	52.5	25.4	osteopenia	osteopenia		14	B	-	36 months	Y	N	N
36	GC	62	m	cirrhosis	alcohol	2.3	98	75	48	3.1	1.7	8.1	4.1	23.4	22.39	osteoporosis	osteoporosis		18	C	-	67 months	Y	N	Y
37	AC	56	m	cirrhosis	nash	2.3	163	81	72	3.1	1.8	7.4	2.7	47.2	30.33	Normal	-		16	B	-	14 months	N	Y	Y
38	SB	54	m	cirrhosis	alcohol	1.6	198	40	38	3.6	1.4	7.9	4.4	21.5	22.47	normal	-		13	B	-	9 months	Y	N	N
39	SK	52	m	cirrhosis	hbv	3.9	105	54	46	2.9	1.8	9.6	2.8	4.6	8.71	osteopenia	osteopenia		20	C	-	38 months	Y	N	Y
40	SK	49	f	cirrhosis	hcv	0.9	113	74	84	3.7	1.3	8.2	3.7	55.4	20.07	osteopenia	osteopenia		9	A	F4	36 months	N	N	N
41	AS	42	m	cirrhosis	alcohol	0.8	98	32	43	3.5	1.1	8.2	3.9	32.3	25.92	Normal	-		9	A	F4	16 months	N	N	N
42	RK	50	m	cirrhosis	alcohol	1.4	179	78	53	3.2	1.7	7.9	3.3	35.8	21.4	normal	-		16	B	-	40 months	Y	N	Y
43	MS	57	m	cirrhosis	alcohol	1.2	99	45	62	3.5	1.4	7.9	3.4	39.1	27.42	osteopenia	osteopenia		10	A	F4	42 months	N	N	N
44	BB	62	m	cirrhosis	alcohol	1.5	102	32	41	3.1	1.6	8.5	4	33.6	28.2	osteoporosis	osteoporosis		14	B	-	50 months	N	N	Y
45	KS	59	m	cirrhosis	hcv	0.8	94	38	47	3.6	1.5	8.1	3.9	68.7	19.2	Normal	-		9	A	-	18 months	N	N	N
46	MS	48	m	cirrhosis	alcohol	2.2	116	102	93	3.4	1.6	8.4	3.6	33	20.8	normal	-		17	B	-	24 months	N	Y	Y
47	RS	47	m	cirrhosis	hcv	1.1	147	82	63	3.3	1.5	8.8	4.1	38.5	22.5	Normal	-		14	A	-	10 months	N	N	N
48	SR	52	f	cirrhosis	nash	1.2	134	58	64	3.4	1.4	8.6	3.4	28.2	35.6	normal	-		9	A	F4	36 months	N	N	N
49	BS	66	m	cirrhosis	hcv	3.9	172	67	52	3.1	1.8	7.8	3.1	40.2	33.8	osteopenia	osteopenia		20	C	-	40 months	N	Y	Y
50	MK	46	m	cirrhosis	alcohol	2.1	181	73	53	3.1	1.8	7.9	2.7	81.1	22.7	normal	-		17	C	-	28 months	N	Y	Y
51	JS	57	m	cirrhosis	hcv	1.5	109	59	68	3.1	1.6	7.8	3.2	37.1	20.5	normal	-		9	A	-	20 months	N	N	Y
52	JK	58	f	cirrhosis	nash	1.3	112	62	59	3.5	1.3	6.9	3.1	33.8	23.5	Normal	-		13	A	F4	26 months	N	N	N
53	HS	59	m	cirrhosis	hcv	0.8	96	47	61	3.6	1.4	7.8	2.9	52.3	25.5	normal	-		10	B	-	30 months	Y	N	N
54	JS	55	m	cirrhosis	alcohol	0.9	165	67	62	3.5	1.3	6.6	3.5	40	18.9	osteopenia	normal		11	B	-	55 months	N	Y	N
55	HS	55	m	cirrhosis	hcv	0.7	113	54	39	3.3	1	7.2	3.7	32.3	23.4	Normal	-		9	A	F4	30 months	N	N	N

Sr. No.	name of the patient	age	sex	diagnosis	aetiology	T.Bilirubin	ALP	SGOT	SGPT	albumin	INR	calcium	phosphorus	PTH	vitamin D3	dexa scan	Dexa at 6	CTP score	MELD	CTP score	Fibroscan	duration of cirrhosis	ascites	HE	coagulopathy
56	DS	55	m	cirrhosis	nash	1.1	121	92	87	3.1	1.4	6.8	2.9	29.9	20.5	osteopenia	osteopenia		11	B	-	47 months	Y	N	N
57	BS	52	m	cirrhosis	alcohol	1.1	132	45	49	3.6	1.5	8.7	2.4	66.8	28.6	normal	-		11	A	F4	6 months	N	N	N
58	PS	50	m	cirrhosis	alcohol	0.8	99	94	71	3.2	1.3	7.9	3.9	45.9	23.4	normal	-		12	B	-	10 months	N	Y	N
59	SK	40	f	cirrhosis	hcv	0.9	124	37	41	3.4	1.3	8.1	3.3	28.7	27	osteopenia	normal		14	B	-	28 months	Y	Y	N
60	D	33	M	cirrhosis	alcohol	1.8	156	38	32	3.1	1.6	7.8	2.9	33.7	25.6	osteopenia	osteopenia		16	B	-	30 months	Y	N	Y
61	RS	31	m	cirrhosis	alcohol	3.4	118	96	50	2.8	1.9	7.8	3.1	42	20.8	osteopenia	normal		18	C	-	18 months	Y	Y	Y
62	GS	50	m	cirrhosis	alcohol	1.8	153	112	97	3.1	2.4	8.3	3.2	54.8	29.8	normal	-		18	B	-	20 months	Y	N	Y
63	DK	50	f	cirrhosis	nash	2.1	188	65	71	2.9	1.5	7.7	3.9	34.9	22.8	normal	-		14	B	-	22 months	Y	N	N
64	SS	58	m	cirrhosis	alcohol	1.6	145	42	36	3.5	1.5	8.1	2.9	48.4	27.5	osteopenia	Normal		13	A	F4	30 months	N	N	N
65	SS	65	m	cirrhosis	nash	5.2	134	42	38	2.1	2.2	9.8	2.7	31.3	40	osteopenia	osteopenia		27	C	-	45 months	N	Y	Y
66	DC	57	m	cirrhosis	nash	1.2	98	68	57	3.4	1.4	8.4	3.9	38.6	20.9	normal	-		10	A	F4	16 months	N	N	N
67	HN	64	m	cirrhosis	alcohol	1.9	142	59	63	2.9	1.5	7.4	4.4	52.5	25.4	osteopenia	normal		14	B	-	26 months	Y	N	N
68	AK	48	m	cirrhosis	hbv	2.3	98	75	48	3.1	1.7	8.1	4.1	23.4	22.39	normal	-		18	C	-	20 months	Y	Y	Y
69	AS	56	m	cirrhosis	nash	2.3	163	81	72	3.1	1.8	7.4	2.7	47.2	30.33	Normal	-		16	B	-	40 months	N	Y	Y
70	MS	50	m	cirrhosis	alcohol	1.6	198	40	38	3.6	1.4	7.9	4.4	21.5	22.47	normal	-		14	B	-	30 months	N	Y	N
71	DS	58	m	cirrhosis	alcohol	3.9	105	54	46	2.9	1.8	9.6	2.8	4.6	8.71	osteoporosis	osteopenia		20	C	-	58 months	Y	Y	Y
72	RK	65	m	cirrhosis	alcohol	0.9	113	74	84	3.7	1.3	8.2	3.7	55.4	20.07	normal	-		9	A	-	30 months	N	N	N
73	GS	60	m	cirrhosis	nash	1.8	98	32	43	3.1	1.7	8.2	3.9	32.3	25.92	Normal	-		14	B	-	24 months	Y	N	Y
74	DL	50	m	cirrhosis	hbv	1.4	179	78	53	3.2	1.7	7.9	3.3	35.8	21.4	normal	-		16	B	-	30 months	Y	N	Y
75	AS	65	m	cirrhosis	alcohol	1.8	99	45	62	2.5	2.4	7.9	3.4	39.1	27.42	osteopenia	osteopenia		20	C	-	40 months	Y	N	Y
76	SM	32	m	cirrhosis	alcohol	3.5	102	32	41	3.1	1.9	8.5	4	33.6	28.2	osteopenia	normal		20	C	-	36 months	N	Y	Y
77	ZS	40	m	cirrhosis	alcohol	1.8	94	38	47	3.2	2.5	8.1	3.9	68.7	19.2	Normal	-		19	C	-	22 months	N	Y	Y
78	JS	64	m	cirrhosis	alcohol	3.2	116	102	93	3.1	2.6	8.4	3.6	33	20.8	normal	-		20	C	-	26 months	Y	N	Y
79	AS	47	m	cirrhosis	hcv	1.1	147	82	63	3.3	1.5	8.8	4.1	38.5	22.5	Normal	-		14	A	F4	30 months	N	N	N
80	KR	46	m	cirrhosis	hcv	3.2	134	58	64	2.7	2.2	8.6	3.4	28.2	35.6	normal	-		18	B	-	19 months	Y	N	Y
81	VS	40	m	cirrhosis	alcohol	3.9	172	67	52	3.1	1.8	7.8	3.1	40.2	33.8	normal	-		20	C	-	23 months	Y	N	Y
82	BS	60	m	cirrhosis	hcv	2.1	181	73	53	3.1	1.8	7.9	2.7	81.1	22.7	osteopenia	normal		17	C	-	33 months	N	Y	Y
83	AS	41	m	cirrhosis	nash	1.5	109	59	68	3.1	1.6	7.8	3.2	37.1	20.5	normal	-		9	A	F4	28 months	N	N	Y
84	HS	58	m	cirrhosis	alcohol	1.3	112	62	59	3.5	1.3	6.9	3.1	33.8	23.5	normal	-		13	A	F4	3 months	Y	N	N
85	BS	39	m	cirrhosis	alcohol	0.8	96	47	61	3.6	1.4	7.8	2.9	52.3	25.5	normal	-		10	B	-	8 months	N	Y	N
86	HS	55	m	cirrhosis	alcohol	0.9	165	67	62	3.5	1.3	6.6	3.5	40	18.9	osteopenia	normal		16	B	-	28 months	Y	Y	N
87	TS	55	m	cirrhosis	hcv	0.7	113	54	39	3.3	1	7.2	3.7	32.3	23.4	Normal	-		9	A	F4	10 months	Y	N	N
88	RS	55	m	cirrhosis	nash	1.1	121	92	87	3.1	1.4	6.8	2.9	29.9	20.5	osteopenia	osteopenia		11	B	-	18 months	Y	N	N
89	CS	52	m	cirrhosis	alcohol	1.1	132	45	49	3.6	1.5	8.7	2.4	66.8	28.6	normal	-		11	A	F4	14 months	N	N	N
90	KS	50	m	cirrhosis	alcohol	0.8	99	94	71	3.2	1.3	7.9	3.9	45.9	23.4	normal	-		12	B	-	6 months	Y	N	N
91	RK	40	f	cirrhosis	hcv	0.9	124	37	41	3.4	1.3	8.1	3.3	28.7	27	osteopenia	normal		14	B	-	19 months	Y	N	N
92	BD	33	M	cirrhosis	alcohol	1.8	156	38	32	3.1	1.6	7.8	2.9	33.7	25.6	osteopenia	osteopenia		16	B	-	30 months	Y	N	Y
93	KS	31	m	cirrhosis	alcohol	3.4	118	96	50	2.8	1.9	7.8	3.1	42	20.8	osteopenia	normal		18	C	-	22 months	Y	N	Y
94	JS	50	m	cirrhosis	alcohol	1.8	153	112	97	3.1	2.4	8.3	3.2	54.8	29.8	normal	-		18	B	-	8 months	N	Y	Y
95	LK	50	f	cirrhosis	nash	2.1	188	65	71	2.9	1.5	7.7	3.9	34.9	22.8	normal	-		14	B	-	13 months	Y	N	N
96	AS	58	m	cirrhosis	alcohol	1.6	145	42	36	3.5	1.5	8.1	2.9	48.4	27.5	osteopenia	Normal		13	A	F4	6 months	Y	N	N

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The Principal,
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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Avinash Singh**, a student of your college for **DM Medical Gastroenterology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

A study of metabolic bone disease in chronic liver disease

Supervisor
Dr. Rajoo S. Chhina
Prof.,
Dept. of
Gastroenterology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Chandan Kakkar
Assoc. Prof.,
Dept. of Radio-diagnosis,
DMCH, Ludhiana.

The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

GASTROENTEROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

APRIL, 2019

DR. AVINASH SINGH

DEPARTMENT OF GASTROENTEROLOGY

DAYANAND MEDICAL COLLEGE AND HOSPITAL, LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE
For the degree of	D.M. (Gastroenterology)
Name of the candidate	Dr. Avinash Singh
Supervisor	Dr. Rajoo S Chhina, Professor, Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana
Co-supervisor	Dr. Chandan Kakkar, Associate Professor, Department of Radiodiagnosis, Dayanand Medical College and Hospital, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Metabolic bone disease (hepatic osteodystrophy) is one the metabolic complication associated with cirrhosis

Aim of Study: 1.To assess the prevalence of metabolic bone disease in liver cirrhosis.

2. To assess the relative prevalence of metabolic bone disease according to etiology of cirrhosis

3. To assess the role of intervention on improvement of BMD

Materials & methods:

The study will be conducted on patients of Liver Cirrhosis admitted in the Inpatient Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana

Clinical Significance: One of the factors which cause a decrease in quality of life, in patients with cirrhosis is decrease in bone mineral density, by increasing the risk of fragile fractures. But most of the patients with metabolic bone disease are not recognized, as there is no proper screening done in these patients.

Keywords: Metabolic Bone Disease, liver cirrhosis

(Signature) Candidate	(Signature) Co-supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled "**A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE**" exist in the Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

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Topic of Thesis	A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE
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5	**TITLE OF THE TOPIC**	A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Cirrhosis (chronic liver disease) represents a disorder which causes progressive hepatic fibrosis characterized by distorted liver architecture and the formation of nodules which are regenerative. Cirrhosis of any cause is usually not reversible when it is in the advanced stages at which the only option available may be liver transplantation. However, in recent times reversal of cirrhosis has been reported in several forms of liver disease following treatment of the underlying cause if detected in its early stages. Patients with cirrhosis are prone to a variety of complications.

Some of the common cause for cirrhosis are[1-3]

1. Alcoholic liver disease
2. Viral hepatitis B & C
3. Autoimmune hepatitis
4. Hereditary hemochromatosis
5. Wilson's disease
6. Alfa-1 antitrypsin deficiency
7. Nonalcoholic fatty liver disease
8. Primary biliary cirrhosis
9. Primary sclerosing cholangitis

Complications of cirrhosis include[1-3]

1. Variceal bleed
2. Hepatic encephalopathy
3. Ascites

4. Spontaneous bacterial peritonitis

5. Hepatorenal syndrome

6. Hepatopulmonary syndrome

7. Hepatocellular carcinoma

Metabolic complications commonly encountered in patients with chronic liver disease are malnutrition, hyponatremia and metabolic bone disease.

Common chronic cholestatic liver disorders are primary sclerosing cholangitis and primary biliary cirrhosis. Hepatic osteodystrophy is known to occur in chronic cholestatic liver diseases. Osteopenic bone disease with fracturing is a complication of chronic cholestatic liver diseases.[1-3] But data regarding the occurrence of metabolic bone disease (hepatic osteodystrophy) in the setting of non cholestatic chronic liver disease is scanty. The development of metabolic bone disease in patients with primary biliary cirrhosis has, in most reports, been directly related to the duration and severity of PBC and to the intensity and duration of jaundice. However, the mechanisms which cause osteodystrophy in patients with PBC are not well understood. The plasma concentrations of vitamin D metabolites and calcium are usually normal.

Biochemical and bone histomorphometric studies suggest that these patients, particularly in the precirrhotic stage, have a "low-turnover" osteoporosis, in which bone formation is inhibited and bone resorption is low or normal, although the mechanism (s) causing these changes are not known.[4-6] It was initially proposed that decreased bile salt flow, leading to malabsorption of vitamin D, was responsible for the development of osteoporosis. However, this hypothesis is most likely incorrect given the observations that the plasma levels of calcidiol (25-hydroxyvitamin D) and calcitriol (1,25 dihydroxyvitamin

D) are normal in PBC patients with osteoporosis and that vitamin D replacement in the group of cases with decreased plasma concentrations will not improve the severity of osteodystrophy.

The diagnosis and severity assessment of osteodystrophy is done by dual energy xray absorptiometry (DEXA).[7-9] It is a non invasive method which measures the bone mineral density. Patients are assisgned T-score and Z-score which are standard deviations below the peak and normal values. This is very useful test to screen the patients for osteodystrophy.

Data regarding the occurrence of metabolic bone disease (hepatic osteodystrophy) in the setting of chronic liver disease is scanty.

6.2 REVIEW OF LITERATURE

Osteodystrophy is a complication in patients with chronic hepatopathy, especially in those affected by chronic cholestasis. Metabolic bone disease usually manifests as osteopenia and osteoporosis. This bone disorder must be evaluated and detected early in all cirrhotic patients to minimize the risk of fractures and improve the quality of life.

EPIDEMIOLOGY

Various international studies have shown the overall incidence of metabolic bone disease in cirrhosis to be between 11% to 48%, and fracture risk due to the bone disease to be between 3%-44%.

Some of the studies which has shown the prevalence are

1. Goral et al. 2010 – frequency of osteodystrophy was 37% in patients with cirrhosis of mixed etiology

2. Wariaghli et al. 2010 – frequency of osteodystrophy was 45.3% in patients with cirrhosis of mixed etiology

3. Loria et al. 2010 – frequency of osteoporosis was 14% and osteopenia was 26% in patients with cirrhosis of viral and alcohol etiology

4. Sokhi et al. 2004 – frequency of osteoporosis was 11.5% and osteopenia was 34.6% in patients cirrhosis of mixed etiology

Chronic liver diseases which are known to cause hepatic osteodystrophy include, cholestatic liver diseases like primary biliary cirrhosis and primary sclerosing cholangitis.[1-3] Hepatic osteodystrophy can also occur in alcoholic cirrhosis and hemochromatosis.

PATHOGENESIS

The pathogenesis of hepatic osteodystrophy in patients with liver cirrhosis has not been completely understood. Several factors which includes- decreased bone formation and increased bone resorption has been recognized in liver cirrhosis. Studies have shown that increase in proinflammatory cytokines, low insulin-like growth factor, and low vitamin K lead to alterations in bone metabolism. Cytokines which are increased in cirrhosis are IL-1, IL-6 and TNF-alfa.[10,15] Serum osteocalcin levels decreases depending on reduction of osteoblast function. A decrease in serum osteocalcin levels and an increase in deoxypyridinoline (DPD) level have been observed in chronic liver disease which is the reason for the low turnover of bone mass.

Other factors responsible for reduced bone mineral deposition are

1. Vitamin K deficiency – is required for osteoblasts to synthesize osteocalcinbone matrix protein. VitaminK deficiency leads to osteopenia in primary biliary cirrhosis and by supplementing it bone loss can be prevented.[7,16,19] 2. IGF-1 deficiency – is required for osteoblast differentiation and proliferation. IGF-1 deficiency occurring in cirrhosis and cholestatic liver disease cause osteoblast dysfunction and osteopenia.[10,19]

3. Hyperbilirubinemia- rise in indirect hyperbilirubinemia has shown impair osteoblast function in animal models.[12,13] But this is not proven in human studies.

Factors which increase the risk of osteodystrophy in cirrhotic patients include[3,6,9]

1. Hypogonadism

2. Vitamin D deficiency

3. Alcohol consumption

4. Chronic steroid treatment

5. Low body mass index

Contribution of vitamin D

Vitamin D has a variety of actions on minerals like calcium, phosphate, and bone metabolism. Vitamin D has an important biological effect on the enterocyte to promote differentiation and causes the intestinal absorption of calcium and phosphorus, which in turn promote bone mineralization. In high vitamin D concentrations and when there is calcium and phosphate deficiency, it also causes stimulation of bone resorption, which helps in the maintaince of supply of these ions to other tissues.[6] Vitamin D is synthesized in the skin with exposure of ultraviolet rays from the sun; ultraviolet rays convert 7-dehydrocholesterol to vitamin D. Anyone with reduced exposure to the sun is prone to vitamin D deficiency. Calcidiol, is formed in the liver before being converted in the kidneys into metabolic active vitamin D (calcitriol).

Gastrointestinal causes of vitamin D deficiency include gastrointestinal malabsorption, associated with disorders of the small intestine, pancreatic diseases resulting in decreased absorption of vitamin D and hepatobiliary disease causes depletion of endogenous 25OHD stores due to abnormal enterohepatic circulation. Malabsorption of vitamin D results as a consequence of steatorrhea, which reduces fat emulsification and chylomicron-facilitated absorption.[11,14,17] Vitamin D deficiency may be associated with rickets or osteomalacia. Patients affected are asymptomatic or may exhibit a reduction in bone volume rather than causing defective bone mineralization.

In liver failure, the levels of 25-OH vitamin D can be reduced due to impaired synthesis. However, liver function needs to be severely compromised for it to cause reduced 25-OH vitamin D synthesis .[3,8,10]

Subclinical vitamin D insufficiency is common in the setting of chronic liver disease and could contribute to the formation of osteoporosis or osteopenia by decreasing absorption of calcium. [6,15,18] Vitamin D deficiency is usually associated with secondary hyperparathyroidism, and there is increased bone turnover and accelerated loss of bone mass. Factors which contribute to vitamin D deficiency include Intestinal malabsorption, altered enterohepatic circulation of vitamin D and reduced skin synthesis in patients with jaundice.

DIAGNOSIS OF METABOLIC BONE DISEASE

Bone mineral density determines the bone strength. Determinants of bone strength, which are not dependent on bone mineral density are bone turn over, microarchitecture of bone like trabacular thickness, cortical thickness and cortical porosity, matrix properties and mineralizaton. Investigation for bone strength will give an insight on the pathogenesis of osteoporosis and osteopenia and gives a better understanding on the treatment given for osteoporosis. Investigations like micro CT and MRI are being developed which can discern individual trabeculae are being developed. With these investigations fracture risk can be accurately gauged. As of now the gold standard for the diagnosis of metabolic bone disease is by DEXA scan. [4,15,20]

Bone mineral density testing — BMD testing is the most commonly used clinical test to diagnose osteoporosis, osteopenia, predict the risk for fracture, and monitor response to therapy. BMD testing can be done on various sites of the body and predict fracture risk. Dual-energy x-ray absorptiometry (DEXA

SCAN) of the spine, hip, and forearm is the method for diagnosis of osteoporosis.[15-20] Serial monitoring of bone mineral density over a period is essential because

1. There has been a strong correlation between bone mineral density measured by DEXA scan and mechanical strength.

2. Studies have shown relationship between bone mineral density by DEXA scan and fracture risk.

3. Randomized clinical trails have shown drug therapy based on the bone mineral density measurement has reduced fracture risk.

4. Accuracy and precision of bone mineral density measured by DEXA scan is very good.

5. Radiation exposure with DEXA scan is very low.

Other methods to analyze bone mineral density

1. Quantitative CT – cortical and trabecular bone can be assessed by determining the volume of bone density. It can measure the bone density of hip and spine. This test can be used to assess the treatment reponse and is also being used is research setup. This method is not used for routine screening. Drawbacks of this test are, it cannot assess the risk of fracture and is a very expensive test.

2. Ultrasound - Patients at risk for osteoporosis can be identified with use of quantitative ultrasound, which is a reasonable predictor of fracture risk. This method can be used in mass screening setup and there is no risk of radiation. But ultrasound threshold cutoff for DEXA score has not been having good sensitivity and specificity. This test cannot be used as confirmatory test .Since

with ultrasound only the peripheral sites can be measured it cannot be used as a tool for follow up of patients who are on therapy.

SITE OF MEASUREMENT OF BONE MINERAL DENSITY

Most common site for measurement of bone mineral density are HIP and SPINE. Spine measurement is more accurate and fracture risk can be assessed more precisely. In patients with cirrhosis and ascites, measurement of bone mineral density of spine can be falsely positive, due to the fluid in the abdomen. In these patients with ascites measurement of bone mineral density from the hip will be useful to assess the risk of fracture.[15,20]

6.3 AIMS AND OBJECTIVES

- To study prevalence of metabolic bone disease in chronic liver disease
- To study the relative prevalence of metabolic bone disease according to etiologies of cirrhosis
- To study the improvement in Bone mineral density after treatment on 6 month follow up.

7. MATERIALS AND METHODS

STUDY DESIGN

This study will be conducted on the patients admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Consecutive patients suffering from chronic liver disease admitted indoors in Department of Gastroenterology, DMC & H will be enrolled for the study.

The patients will be assessed for metabolic bone disease by measuring Sr Vit D3 level, Sr Parathyroid hormone, Sr Calcium, and DEXA Scan for osteoporosis and osteopenia at the time of enrolment and the one who found to be having metabolic bone disease will be given treatment in the form of calcium, vit D3 and bisphosphonates, and evaluated again after 6 months for improvement of BMD.

7.1 SOURCES OF DATA

Consecutive patients suffering from Chronic liver disease admitted indoors in Department of Gastroenterology, DMC & H will be enrolled for the study.

7.2 METHODS OF COLLECTION OF DATA

DATA COLLECTION

Confirmed and newly diagnosed cases of Chronic liver disease will be enrolled.

MATERIAL AND METHODS

Study design – Observational Study

Subjects:

Patients with the diagnosis of chronic liver disease of all etiologies attending our department will be included in this study. All the patients will explained in detail about the study, and an informed consent will be obtained.

INCLUSION CRITERIA

1. Liver cirrhosis of all etiologies

EXCLUSION CRITERIA

1. Patients who were on calcium supplements and vitamin D
2. Patients on medications which affect bone mineral density
3. Postmenopausal women
4. Patients with coexistent chronic kidney disease

DURATION OF STUDY

The study period will start from March 2019 to Oct 2019 with follow up period of 6 months till March 2020.

OUTCOME

Primary outcome

- To determine prevalence of metabolic bone disease in cirrhosis

Secondary outcome

- To determine the response of intervention on Bone mineral density
- To determine the severity of metabolic bone disease according to severity of liver disease

STATISTICAL ANALYSIS

Continuous variables will be expressed as median (range). The Mann–Whitney U test was used to evaluate the significance of differences in median values. The chi-square test or Fisher's exact test will be used to compare differences in categorical variables between groups. Possible predictors of osteodystrophy will be evaluated first with a univariate logistic regression analysis, and a multivariate logistic analysis will be then conducted with variables that were significant in the univariate analysis. The prognostic

factors of patients with liver cirrhosis will be analyzed by a Cox proportional hazards regression model. The correlation between CTP, MELD and osteodystrophy will be done using Pearson correlation coefficient. All analyses will be carried out using SPSS version 21 software. $P < 0.05$ was considered statistically significant.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

- Yes, the study requires both investigations and interventions.

  Pre treatment tests include

  - Complete blood counts, Erythrocyte Sedimentation Rate
  - LFT, ANA ,ASMA , ANTI LKM1
  - Serum calcium , vitamin D, Parathyroid hormone
  - Serum creatinine
  - Random blood sugar
  - Anti HCV antibody, HBs Antigen, Anti HIV antibody
  - Ultrasound whole abdomen
  - UGIE
  - Histology if available
  - DEXA Scan

  - The following intervention will be carried out

    Calcium, Vit D3 and Bisphosphonates supplements to patients.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes, Attached along with.

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PROFORMA

Name:	**S.NO**
Address:	**MRD.NO**
Mobile No:	**Age/Sex:**
Date of Admission:	**Date of Discharge:**

1) HISTORY

1) Presenting complaints

Symptoms	*Duration*
1)	
2)	
3)	

1.1) ***Past history*** - H/o Cirrhosis since

1.2) H/o Bleed

Signature of Candidate **Signature of Supervisor**

H/o Ascites

H/o Hepatic encephalopathy

H/o Diabetes, Hypertension

H/o Ischemic heart disease,

DIAGNOSIS:

Lab Investigation:

Parameter	*Baseline*
CBC	
LFT	
RFT	
VITAMIN D3	
CALCIUM	
PHOSPHOROUS	
VIRAL MARKERS	
DEXA SCAN	

Signature of Candidate **Signature of Supervisor**

CTP Score:

MELD Score:

Chest X Ray PA view -

Ultrasound abdomen/CT abdomen-

Upper GI Endoscopy-

Patient Follow up at 6 months:

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

I.....D/o, W/o, S/o..... .....am willing to participate in the study "**A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE**". The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____ निवासी _____ इस शोधकार्य " A STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE " में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ _____

ਮੈਂ _____ ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ _____ ਵਾਸੀ _____ ਇਸ ਖੋਜ "ਅ STUDY OF METABOLIC BONE DISEASE IN CHRONIC LIVER DISEASE" ਵਿੱਚ ਹਿੱਸਾ ਲੇਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈਂ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈਂ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ/ਚਾਹੁੰਦੀ ਹਾਂ ਕਿ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂੰ ਕਿਸੇ ਵੀ ਤਰ੍ਹਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀਂ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂਮ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕਿ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਵਿੱਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਯਕੀਨ ਹੈ ਕਿ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ-ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈਂ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇਂ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀਂ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ